Schizophrenia: A major risk factor for cardiovascular disease

Schizophrenia, a debilitating mental illness characterized by hallucinations, delusions, and in many cases, impaired cognitive and occupational functioning, is a life-shortening disease (Newcomer, 2007). People with schizophrenia and other types of severe mental illness (SMI) die earlier than mentally healthy people—estimates range from 10–15 years (White et al, 2009) to 25–30 years sooner (Newcomer and Hennekens, 2007). Life expectancy in schizophrenia has been calculated as approximately 30% shorter than that of the general population in the US (Fagiolini and Goracci, 2009). Although suicide is ‘the single major cause of death’ in schizophrenia (Pompili et al, 2009), with an estimated lifetime prevalence of 5.6% (Palmer et al, 2005), the rise in standard mortality rates (SMR) is mainly accounted for by the range of physical health problems (Auquier et al, 2007), in particular cardiovascular disease. The higher SMRs for people with schizophrenia compared to the general population are found across different cultures (Ösby et al, 2000; Brown et al, 2000; Auquier et al, 2007) (Table 1).

In essence, people with schizophrenia die of the same diseases as the rest of the population, but they die more frequently and at a younger age. Many of these may be preventable by modifications in lifestyle. The reduced motivation and functional decline seen in schizophrenia are less dramatic than the voices or delusions that can be experienced, but do damage to physical health in terms of poor diet, infrequent physical exercise, increased smoking rates, comorbid substance abuse and high levels of psychological stress (Brown et al, 1999). All of these, plus the high rates of depression in schizophrenia, which is also an independent risk factor for heart disease, compound a pre-existing vulnerability to metabolic disorders in schizophrenia.

Yet despite these frightening statistics, many people with schizophrenia have difficulty in accessing care. A stark illustration of this is that although the rates of cancer in schizophrenia equal those in the general population, people with schizophrenia are twice as likely to die of cancer (Lambert et al, 2003). Nearly half of all people with schizophrenia have a comorbid medical condition, which is often not diagnosed, or is misdiagnosed (Goldman, 1999).

People with SMI are more likely to suffer from diabetes (Newcomer et al, 2002; Ryan et al, 2003; Newcomer, 2007), cardiovascular disorders (McIntyre, 2009), and abnormalities in their hypothalamic-pituitary-adrenal axis (HPA) functioning (Ryan et al, 2004). Additionally, people with SMI tend to have higher levels of blood cholesterol and triglycerides, increasing their cardiovascular risk (Brown et al, 1999; Fleischhacker et al, 2008). The ‘metabolic syndrome’ (a cluster of symptoms including hypertension, central obesity, hyperglycaemia and dyslipidaemia that is known to increase the risk of cardiovascular

### Table 1. Standardized mortality rates in schizophrenia

<table>
<thead>
<tr>
<th>SMR</th>
<th>Country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.98</td>
<td>UK</td>
<td>Brown et al, 2000</td>
</tr>
<tr>
<td>2.6</td>
<td>Sweden</td>
<td>Ösby et al, 2000</td>
</tr>
<tr>
<td>2.6</td>
<td>Canada</td>
<td>Newman and Bland, 1991</td>
</tr>
<tr>
<td>1.59</td>
<td>France</td>
<td>Casadebaig and Phillipe, 1999</td>
</tr>
</tbody>
</table>

### Abstract

People with schizophrenia, bipolar disorder and other severe mental illnesses (SMIs) die earlier than mentally healthy people, largely because of the range of physical health problems they experience. This article reviews the factors behind the increased risk of cardiovascular disease in people with SMIs. These include lifestyle factors compounding a pre-existing vulnerability to metabolic disorders and also side-effects of antipsychotic drugs used in treatment of their condition.

Examples from the literature of physical and behavioural strategies that have been trialled to prevent or manage this problem are discussed.

### Key Words
- Metabolic disorders
- Cardiovascular risk
- Mental health

Submitted for peer review 4 April 2011. Accepted for publication 20 April 2011.
Conflict of interest: Fiona Gaughran has received honoraria as a consultant, scientific advisor or speaker from Bristol Myers Squibb, Partnerships in Care and Roche, and has family connections to Lilly and GSK.
events), is approximately twice as prevalent in people with schizophrenia as in the general population (L'Italien et al, 2007). Apart from the distress and reduced quality of life caused by these physical health problems themselves, the economic costs incurred by managing these comorbidities is and will continue to be a considerable burden on health services (Jerrell et al, 2010), making cardiovascular risk in schizophrenia a current service priority.

**Antipsychotic drugs and increased morbidity and mortality**

Many of the antipsychotic drugs used to treat schizophrenia are associated with the emergence of cardiovascular risk factors. Antipsychotic-induced weight gain occurs in at least 50% of patients treated with antipsychotics (Baptista et al, 1999), and impacts on cardiovascular risk, self-esteem and adherence to treatment. Individual antipsychotic drugs have differing effects on weight gain as well as on glucose and lipid metabolism (Allison et al, 1999). The antipsychotics with the highest propensity for weight gain are clozapine and olanzapine (Allison et al, 1999; Simpson et al, 2001; Bobes et al, 2003; Treuer et al, 2009). The mechanisms driving antipsychotic-induced weight gain are not altogether certain, but appear to be related to neurotransmitter blockade, particularly at the histamine receptor, the dopamine receptors and the serotonin 5HT2c receptor. The US Food and Drug Administration (FDA) has agreed with the American Diabetes Association and the American Psychiatric Association consensus guidelines (American Diabetes Association et al, 2004) on three tiers of weight gain and metabolic risk for antipsychotic drugs (Table 2).

The incidence and cumulative prevalence rates of four cardiometabolic risk factors over three years in patients taking antipsychotic drugs are as follows: non-insulin dependent diabetes mellitus are 23%; obesity 13.3%; dyslipidaemia 20.9%; and hypertension 41.8% (Jerrell et al, 2010). Thus, although people with schizophrenia have a pre-existing vulnerability to cardiovascular and metabolic disease, treatment–emergent adverse effects occur in a significant number of patients.

The gold-standard drug in treatment-resistant psychosis, clozapine, causes high levels of weight gain, to the point where earlier workers such as Fontaine et al (2001) raised the concern as to whether the raised cardiovascular risk may outweigh the reduction in suicide rates. Happily, a recent large population-based study from Finland has shown that there is a reduction in all-cause mortality in people with schizophrenia treated with clozapine when compared with those treated with other antipsychotics or those people with schizophrenia who had not received treatment with an antipsychotic drug (Tiibonen et al, 2009). Nevertheless, people on clozapine and other antipsychotic drugs should be monitored for emergence of modifiable cardiovascular risk factors.

Consensus guidelines from bodies such as the National Institute for Health and Clinical Excellence (NICE) (2009), the American Psychiatric Association (American Diabetes Association et al, 2004) and the recent ‘position statement’ from the European Psychiatric Association (de Hert et al, 2009) recommend regular monitoring of weight, blood pressure, glucose, cholesterol and triglycerides levels, for people taking antipsychotics.

**QTc prolongation**

Many antipsychotic drugs are known to lengthen the QTc interval, which can increase the risk for the potentially fatal arrhythmia known as Torsades-de Points. Up to 4.5% of patients receiving antipsychotics may have a prolonged QTc interval; some drugs being more likely to cause this than others. Haloperidol, thioridazine (withdrawn in the UK for this reason), and sertindole are all strongly associated with QTc prolongation (Taylor et al, 2009). Risk factors for QTc prolongation are existing cardiovascular disease, female sex, treatment with antipsychotics and older age (Yang et al, 2011), as well as a pre-morbid longer QTc, which some people have naturally. Current NICE (2009) guidelines and the Maudsley Prescribing Guidelines (Taylor et al, 2009) recommend baseline ECGs for patients who are starting antipsychotics, and on admission to hospital as well as for people on doses exceeding the BNF maximum, as the changes in QTc are dose-related.

**Modifiable risk factors for cardiovascular disease**

The World Health Organization has identified the top six modifiable risk factors worldwide for early mortality as hypertension, smoking, raised glucose, physical inactivity, obesity and dyslipidaemia (Wildgust and Beary, 2010). All of these risk factors occur at higher rates in people with SMI than in the general population and hypertension, hyperglycaemia and dyslipidaemia, being less ‘visible’ than the others, tend to not be identified and/or not treated. A combination of decreased access to general health care, a lack of awareness, and the nature of SMI itself in terms of

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Risk for weight gain</th>
<th>Risk for diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>Differential findings</td>
</tr>
<tr>
<td>Risperidone (and Paliperidone)</td>
<td>++</td>
<td>Differential findings</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Ziprasidone (not available in the UK)</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

*Amisulpride, which is not available in the USA, probably has a higher risk than aripiprazole and ziprasidone, but lower than quetiapine and risperidone, and would constitute a fourth tier: ‘+’)}
social marginalization, and impaired cognitive and social functioning, are all contributing factors to this (Lambert et al, 2003). However, even when these conditions are indentified and treated, adding antihypertensives, hypoglycaemic agents and/or statins to an often already complex regime compounds the ‘pill burden’, potentially lowering compliance rates (Frishman, 2007). Deterioration in mental health status often results in poorer management of long-term health conditions, thus adding to the longer-term risk. Programmes that can address or prevent modifiable risk factors are likely to be more beneficial than waiting until ‘the horse has bolted’ and there is an established disease or dysregulation.

Dyslipidaemia is one of the most significant risks for cardiovascular disease (Chapman, 2010). Prevalence rates in the US general population are as high as 35% in people aged over 20 years (Centres for Disease Control and Prevention, 2011). In people with SMI, the figures are much higher; baseline data on 1460 patients from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that 998 (68.4%) had dyslipidaemia, only 12% of whom were receiving treatment (Nasrallah et al, 2006). In the UK, even though patients with SMI may visit their GP on a regular basis, few are screened for diabetes or have had lipid profiles done (Gupta and Craig, 2009).

Many people with SMI are cigarette smokers: nearly 90% in the USA compared to 25–30% of the general population (Schizophrenia.com, 2006). Smoking is one of the most obvious modifiable risk factors for heart disease. Bobes et al (2010) analysed the smoking-associated risks for cardiovascular disease in 1704 patients with SMI over 10 years, and predicted that smoking cessation would result in an almost 90% reduction in the risk of a cardiovascular event over the next 10 years.

Addressing the problem of cardiovascular comorbidity in schizophrenia

Awareness of the extent of physical comorbidity in schizophrenia has grown over the past decade, and a number of physical and behavioural strategies to prevent or manage this problem have been trialled, with varying degrees of success. Stahl et al (2009) described weight gain and obesity as the first step on the ‘metabolic highway’ towards the endpoint of premature death from cardiovascular disease. Interventions designed to treat obesity have been the most widely published, possibly because it is more visible and stigmatising than other ‘hidden’ risk factors such as dyslipidaemia and hyperglycaemia, but also because effecting weight loss may prevent progression to diabetes and cardiovascular disease.

A randomized, controlled trial of 550 (non-psychotic) people with impaired glucose tolerance (IGT), found that modest lifestyle changes, including gentle exercise, diet modifications and moderate weight loss (mean 4.2 kg after 1 year, and mean 3.5 kg after 2 years) were enough to prevent 58% of the intervention group from developing diabetes over a 4-year period (Tuomilehto et al, 2001). Overall weight loss was significant at both time points, and there were significant differences in weight loss and the incidence of diabetes prevention between the intervention and control groups. The study used individualized counselling and nutritional advice to produce sustainable lifestyle changes. It is reasonable to speculate that tailored approaches may be needed for people with SMI, for example where symptoms interfere with engagement with interventions.

Ohlsen et al (2004) used a combination of motivational interviewing, individual diet modification/planning and physical exercise in a sample of 46 overweight patients with SMI to induce weight loss. A UK-wide industry-sponsored intervention, the ‘Well Being Support Programme’, used nurse advisors to monitor physical health and provide advice on diet, physical activity and smoking cessation in 966 people with SMI over a 2-year period in seven different mental health centres across the UK. There was an 80% completion rate. However, although significant improvements were seen in smoking and levels of physical activity by the end of the study, sizeable cardiovascular risk remained: 45% of subjects still smoked, 26% had hypertension, and 81% had a body mass index (BMI) >25. In a subset of patients from this study, Ohlsen et al (2005) found significant improvements in diet (less fat, more fibre) over 2 years, but no significant weight loss or reduction in blood pressure. Thus, addressing the risks, monitoring and providing advice on lifestyle appears to have a variable effect, and is very ‘individual’ in terms of response.

Pendlebury et al (2007) reported 5-year follow-up on a group weight-management intervention lasting at least a year for motivated, overweight antipsychotic-treated patients who wanted to lose weight. Data was available for 41 patients at 1 year. Weight loss was significant at 1 year and maintained at 5 years’ follow-up and correlated with the number of sessions attended. The intervention used group support to facilitate simple lifestyle changes such as improving diet and increasing physical activity. Psychosocial trials using cognitive behaviour therapy to effect weight loss (Umbricht et al, 2001; Weber and Wyne, 2006) have also reported wide variability in response, and no long-term follow-up data is available for these studies. Some studies using group therapy have proved useful, as peer support may be of more benefit than advice from a health professional.

A health promotion intervention based on motivational interviewing techniques combined with cognitive behaviour therapy (IMPACT HPI) is being evaluated as part of an ongoing National Institute for Health Research (NIHR) funded randomized controlled trial, the IMPACT RCT. Motivational interviewing has been used successfully in treating addictions and also as a tool to effect weight loss with variable results (Ohlsen et al, 2004). IMPACT HPI is aiming to encourage positive lifestyle changes such as substance use reduction, smoking cessation, improvement in the quality of diet and increase in physical activity—thereby reducing cardiovascular risk—by training care coordi-
nators in community mental health teams in several NHS trusts to deliver the intervention to their client groups. The RCT will determine the effect of the IMPACT HPI on quality of life in service users with SMI, and assess the cost effectiveness of this intervention compared to treatment as usual. Embedding such interventions in real-world clinical practice may prove to be an effective method of identifying and addressing risk factors for cardiovascular disease in the severely mentally ill, and may better ensure that regular physical monitoring is carried out.

Conclusions
SMI, particularly schizophrenia, is strongly associated with reduced life expectancy, and cardiovascular disease is the leading cause of premature death in this group. While this population appears to be inherently vulnerable to metabolic dysregulation and cardiovascular disease, and is rendered even more vulnerable by long term antipsychotic medication, significant improvements in levels of morbidity as well as increased life expectancy could very likely be achieved by addressing modifiable risk factors such as smoking, diet and physical activity. In the UK at present this is a priority clinical field not just for psychiatrists but also for primary and secondary level physical health-care providers. An emphasis on structured, regular, and ongoing monitoring of weight and blood pressure, as well as screening for diabetes, hypercholesterolemia and dyslipidaemia according to agreed guidelines would alert health-care professionals to patients at risk, and allow for access to advice about lifestyle changes such as smoking cessation, improved diet, substance misuse and exercise.

Risk Factors

Key Points

- Physical comorbidity, in particular cardiovascular disease, is a major cause of early death in people with schizophrenia
- The reduced motivation and functional decline seen in schizophrenia are less dramatic than the voices or delusions that can be experienced, but do damage to physical health in terms of unhealthy lifestyle behaviours
- Antipsychotic-induced weight gain occurs in at least 50% of patients treated with antipsychotics
- Consensus guidelines recommend regular monitoring of weight, blood pressure, glucose, cholesterol and triglycerides levels, and ECGs for people taking antipsychotics
- Of the physical and behavioural strategies to prevent or manage the comorbidity, interventions designed to treat obesity have been the most widely published.

pituitary-adrenal overactivity in first episode, drug-naïve patients with schizophrenia. Psychoneuroendocrinology 29(8): 1065–70
Wildgust HJ, Beary M (2010) Are there modifiable risk factors which will reduce the excess mortality in schizophrenia? J Psychopharmacol 24(4 Suppl): 37–50