Introduction

People with severe mental illnesses (SMI), such as schizophrenia or bipolar disorder, have a reduced life expectancy compared to the general population [1-7]. They have a 2-3 fold increased risk of dying and that the mortality gap associated with mental illness compared to the general population has widened in recent decades [7]. People with severe mental illness have nearly twice the normal risk of dying from cardiovascular disease (CVD) [1-7].

In the psychiatric community this has lead in recent years to an increased interest in physical illnesses in people with SMI, specifically with regard to CVD risk.

Cardio-metabolic Risk in SMI

People with SMI are more likely to be overweight, to smoke, and to have hyperglycemia/diabetes, hypertension, and dyslipidemia [8-15] (Table1). In part these cardio-metabolic risk factors are attributable to an unhealthy lifestyle, including poor diet and sedentary behavior. But over recent years it has become apparent that antipsychotic agents (AP) can have a negative impact on some of the modifiable risk factors [8-15] (Table 2). Part of this negative impact can be explained by the liability of some antipsychotics to induce significant weight gain [16-18]. A recent study indicates that these metabolic changes are dose independent [19].

Metabolic syndrome (MetS) brings together a series of abnormal clinical and metabolic findings which are predictive of CV risk, though there is continuing debate around the use of the term [20-29]. The concept has found its way into the psychiatric literature helping psychiatric clinicians to focus more on CVD risk in patients treated with AP [30-37]. To date 40 different studies have yielded consistent results showing elevated rates of MetS in both patients with schizophrenia and bipolar disorder [32].

In the largest study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, approximately one third of patients in CATIE met National Cholesterol Education Program (NCEP) criteria for metabolic syndrome at baseline [33-34]. A troubling finding was that 88% of patients with dyslipidemia were not receiving treatment, as were 62% of the hypertensive patients and 38% of those with diabetes [35]. Some antipsychotic agents were associated with more significant adverse effects on weight, lipids, and glucose metabolism than others [34].

A large Belgian study found similar rates of MetS, which were 2 to 3 fold higher than in an age-adjusted population sample [32,36]. The prevalence of diabetes per age-band was 4-5 times higher in schizophrenia patients than in the general population.

In a recent study of metabolic syndrome in patients diagnosed with schizophrenia from 2000-2006 compared to 1984-1995, those started on second generation antipsychotics (SGA) had over twice the rate of new incident cases of metabolic syndrome after three years, compared to those treated with first generation antipsychotic agents (27.8% versus 9.8%) [37]. In patients
without metabolic syndrome at baseline, the risk of developing this combination of metabolic abnormalities was significantly greater in patients started on SGA (odds ratio 3.6) [37].

The majority of evidence is in patients with schizophrenia who are taking antipsychotic medication. There is, however, emerging evidence that there is an increase of modifiable CV risk factors, such as diabetes, in patients with bipolar disorder and in those with a history of depression and/or taking drugs to treat depression [38-40]. We recently reported on elevated rates of MetS in bipolar patients [41]. In another study we found that psychiatric diagnosis independent of medication and other confounding factors independently influenced the risk for MetS, with people with schizoaffective disorder having higher risk than people with schizophrenia or bipolar disorder [42].

Until recently there was no data on the safety and efficacy of statins in patients also exposed to antipsychotics. In patients with schizophrenia statins were an effective and safe treatment for severe dyslipidemia but they did not succeed in reversing MetS [43-44].

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 [45-48].

Guidelines for Screening and Monitoring

Prevention should be of key importance. Clinicians should take into account both the present CVD risk as well as the metabolic risk profile of the antipsychotic chosen. Diet and lifestyle interventions should be started early after treatment initiation.

Despite the 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 [3,49]. There is a lack of consensus over who should take responsibility for the general healthcare needs of mental health patients which has resulted in a continuing failure to provide appropriate services. General health care needs in this population were commonly neglected and psychiatrists mainly focus on efficacy of treatment of psychotic symptoms [3,5,14-15].

Over recent years both national and international groups have developed screening and monitoring guidelines [9,50-56] but these have not made their way to routine clinical care for patients [57-58].

If a patient develops metabolic abnormalities (e.g. weight gain, increased blood pressure, glucose, or lipid levels) following initiation of antipsychotic therapy, consideration should be given to switching the patients to an SGA which has not been associated with significant weight gain or diabetes. Initiation of appropriate blood pressure, glucose, or lipid lowering therapy should also be considered, in consultation with the patient’s GP when that is possible, or with a specialist physician when this is considered appropriate [3,54].

A European current update of screening and monitoring guidance is being written by the EPA in collaboration with ESAD and ESC [59,60].

Conclusions

Mets and other CVD risk factors are highly prevalent in people with SMI. The psychiatrist needs to be aware of the potential metabolic side-effects of antipsychotic medication and to include them in the risk/benefit assessment when choosing a specific antipsychotic. He should also be
responsible for the implementation of the necessary screening assessments and referral for treatment of any physical illness. Multidisciplinary assessment of psychiatric and medical conditions is needed. The somatic treatments offered to people with severe and enduring mental illness should be at par with general health care in the non-psychiatrically ill population [3,49].

References


Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. 2007. European guidelines on

Table 1: Estimated Prevalence and RR of Modifiable Cardiovascular Disease Risk Factors in Schizophrenia and Bipolar Disorder Compared to the General Population [8]

<table>
<thead>
<tr>
<th>Modifiable Risk Factors</th>
<th>Schizophrenia</th>
<th>Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>45%-55% RR: 1.5-2</td>
<td>21%-49% RR: 1-2</td>
</tr>
<tr>
<td>Smoking</td>
<td>50%-80% RR: 2-3</td>
<td>54%-68% RR: 2-3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10%-15% RR: 2</td>
<td>8%-17% RR: 1.5-2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19%-58% RR: 2-3</td>
<td>35%-61% RR: 2-3</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>25%-69% RR: ≤5</td>
<td>23%-38% RR: ≤3</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>37%-63% RR: 2-3</td>
<td>30%-49% RR: 1.5-2</td>
</tr>
</tbody>
</table>

RR=relative risk.
Table 2: Second generation antipsychotic agents and metabolic abnormalities [9,13,54]

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Weight gain</th>
<th>Risk for diabetes</th>
<th>Worsening lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>±</td>
<td>No report</td>
<td>No report</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>±</td>
<td>No report</td>
<td>No report</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>±</td>
<td>No report</td>
<td>No report</td>
</tr>
</tbody>
</table>

* Cases of diabetes have now been reported with all the SGAs, but the difference in relative risk remains the same; no report: at moment of publication no cases reported, since then cases of diabetes have been reported with all SGA.