Metabolic risk factors in first-episode schizophrenia: baseline prevalence and course analysed from the European First-Episode Schizophrenia Trial

W. Wolfgang Fleischhacker*, Cynthia O. Siu*, Robert Bodén, Elizabeth Pappadopulos, Onur N. Karayal, René S. Kahn and the EUFEST study group

1 Department of Biological Psychiatry, Medical University Innsbruck, Innsbruck, Austria
2 Data Power Inc., New Jersey, USA
3 Department of Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden
4 Pfizer Inc., New York, USA
5 Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, The Netherlands

Abstract

Available data on antipsychotic-induced metabolic risks are often constrained by potential confounding effects due to prior antipsychotic treatment. In this study, we assessed the baseline prevalence of metabolic abnormalities and changes following treatment with five commonly-used antipsychotic drugs (haloperidol, amisulpride, olanzapine, quetiapine or ziprasidone) in first-episode, partially antipsychotic-naive patients with schizophrenia in the European first-episode schizophrenia trial (EUFEST). Overall baseline prevalence of metabolic syndrome (MetS) was 6.0%, with similar rates observed in the antipsychotic-naive patients (5.7%, 9/157) and in the other patients with only a brief prior exposure to antipsychotics (6.1%, 20/326). These results are consistent with the MetS prevalence rate estimated in a general population of similar age. Examination of individual risk factors showed 58.5% of subjects had one or more elevated metabolic risks at baseline: 28.5% demonstrated suboptimal HDL; 17.7% hypertriglyceridemia; 8.2% abdominal obesity; 7.3% hyperglycaemia. Increase in body weight (kg/month) occurred in patients treated with haloperidol (0.62 S.E. 0.11), amisulpride (0.76 S.E. 0.08), olanzapine (0.98 S.E. 0.07) and quetiapine (0.58 S.E. 0.09), which was significantly greater than that in the ziprasidone group (0.18 S.E. 0.10). The incidence rate of new diabetes cases over a 52-wk follow-up period was 0.82% (4/488). More patients experienced worsening rather than improvement of hypertriglyceridemia or hyperglycaemia in all treatment groups. Our findings suggest that in first-episode, partially antipsychotic-naive patients, the baseline prevalence rate of MetS appears to be no higher than that in the general population, but serious underlying individual risk factors nevertheless existed.

Received 17 February 2012; Reviewed 29 April 2012; Revised 3 September 2012; Accepted 4 September 2012; First published online 20 December 2012

Key words: Antipsychotic, antipsychotic-naive, first episode, metabolic syndrome, schizophrenia.

Introduction

Patients with severe mental illness often suffer from excessive medical co-morbidities and mortality when compared to the general population (Fleischhacker et al., 2008). Recent mortality statistics in patients with schizophrenia suggest a 2.5-fold increase in mortality relative to the general population (Saha et al., 2007). Despite slight variations in interpretation and controversies over its clinical significance, the cluster of cardiovascular risk factors commonly referred to as metabolic syndrome (MetS; Eckel et al., 2005; Reaven, 2005; Kahn, 2008) has also become a public health issue in caring for patients with severe mental illness (McEvoy et al., 2005; Meyer et al., 2005). MetS has been found to be highly prevalent among patients with schizophrenia due to the combined effects of genetic predisposition (Hasnain et al., 2010), negative psychopathology (Bobes et al., 2010), unhealthy diet and sedentary lifestyle (Bobes et al., 2007) and prior antipsychotic exposure and/or current antipsychotic treatment (De Hert et al., 2006; Newcomer and Hennekens, 2007; Correll et al., 2009; Mitchell et al., 2011; De Hert et al., 2012). A recent systematic review suggested the prevalence rate of MetS was similar in first-episode (9.9%) and unmedicated (9.8%) patients with schizophrenia (Mitchell et al., 2012a), which were lower.
than the MetS rate of 35.3% in chronic medicated patients (Mitchell et al., 2011). Previous studies have also reported a higher MetS prevalence in female than in male patients, primarily attributable to more frequent abdominal obesity in the former (De Hert et al., 2006).

Existing clinical studies on patients with early psychosis suggest that younger patients or those in the early stages of illness may be more vulnerable to the adverse weight and metabolic effects associated with some antipsychotic treatments than their older or more chronic counterparts (Patel et al., 2009). Some second-generation antipsychotics (SGAs), most notably clozapine and olanzapine, have been shown to be associated with more undesirable weight change as well as glucose and lipid metabolism side-effects that can contribute to MetS (Lieberman et al., 2005; De Hert et al., 2006; Newcomer and Haupt, 2006; Fleischhacker et al., 2008; Saddichha et al., 2008; Bertelsen et al., 2009). Accurate assessment of such adverse side-effects attributable to different antipsychotic treatments would best be performed in a population of first-episode and drug-naive schizophrenia patients. For such subjects, there would be less confounding effects caused by prior antipsychotic treatment and more adequate characterization of the pre-existing baseline risk factors.

The European first-episode schizophrenia trial (EUFEST) offers a unique opportunity to extend previous research by investigating the prevalence of metabolic abnormalities in schizophrenia and the risks of diabetes and cardiovascular disease before and following treatment with five commonly-used antipsychotic drugs in first-episode, partially antipsychotic-naive, patients with schizophrenia.

Method

Subjects

The study design and methods of the 1-yr open-label EUFEST study have been published previously (Fleischhacker et al., 2005; Kahn et al., 2008). Eligible subjects aged 18–40 yr met the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) for schizophrenia, schizophréniform disorder, or schizoaffective disorder. Diagnoses were reconfirmed by the Mini-international Neuropsychiatric Interview plus (MINI plus; Sheehan et al., 1998). The first-episode or partially antipsychotic-naive study population was defined as having \( < 2 \) yr since the onset of positive symptoms and use of any antipsychotic drug for \( < 2 \) wk in the previous year or for \( < 6 \) wk at any time. Patients were excluded if known to have intolerance to one of the study drugs, or if they were contraindicated for any of the study drugs, as stated in the (local) package inserts. All participants – or their legal representatives – provided written informed consent. The trial complied with the Declarations of Helsinki and was approved by the ethics committees at participating centres. The Julius Centre for Health Sciences and Primary Care in Utrecht, the Netherlands, monitored the trial according to good clinical practice and the International Conference on Harmonization guidelines.

Study assessments and analysis criteria for metabolic syndrome

At screening, a medical history was taken and a physical examination was performed. Body weight (BW) and waist circumference (WC) were assessed at baseline and at 13, 26, 39, and 52 wk. Laboratory data (fasting glucose, cholesterol, HDL and LDL, fasting insulin, triglycerides and prolactin) were assessed at baseline and at 26 and 52 wk. Insulin resistance (IR) was calculated using the homeostatic model assessment (HOMA; Matthews et al., 1985). Details of the analysis criteria for individual risk factors and overall MetS according to the National Cholesterol Education Program’s Adult Treatment Panel IIIA (NCEP-ATP-III), American Heart Association (AHA) and International Diabetes Foundation (IDF) consensus definitions, as well as some baseline demographics of male and female EUFEST subjects are presented. Diabetes was considered present in the study if the participant was under treatment with insulin or oral hypoglycaemic agents, or if fasting blood glucose exceeded 126 mg/dl or 6.993 mmol/l at the screening baseline.

Statistical analysis

Baseline data were used to identify subjects with elevations in cardiometabolic risks. Treatment effects on the time-courses of change in metabolic risk factors were evaluated using categorical treatment \( \times \) visit interaction effect terms in a mixed effects model, with adjustment for baseline values. The categorical treatment \( \times \) visit interaction term permitted an examination of the treatment effect at individual visits without making the parametric linear model assumption on the shape and functional of the trajectory. Random variability due to countries and subjects (nested within countries) were accounted for in the unstructured covariance model for random effects (Willett et al., 1998; Fitzmaurice et al., 2004). Mixed effects models were used in the analysis to accommodate subjects with missing data under the usual missing at random assumption, i.e. missing values such as BW were ignorable (unrelated to the reason for drop-out) and could be accurately predicted by the other observed data using adequate models for both fixed and random effects (covariance structures; Fitzmaurice et al., 2004; Potkin and Siu, 2009). We also performed analyses of changes from baseline to the 1-yr last observation carried forward (LOCF) end-point and compared them across the treatment groups. Logistic regression was applied to evaluate the occurrence of worsening in individual risk factors (a shift from normal to abnormal state) after adjusting,
for country effects. All analyses were two-tailed with \( \alpha \) set at 0.05. Adjustments for multiple comparisons were not performed in this exploratory analysis.

**Results**

**Baseline cardiovascular and metabolic risk prevalence**

Of 498 randomized subjects in the EUFEST study, MetS based on ATP-III/AHA criteria could be assessed for 488 patients using the baseline data, with an overall prevalence of 5.9% (29/488; Table 1). Among 440 subjects (48 subjects with missing WC) with available data for evaluation according to the IDF MetS criteria (non-missing WC measurement and two additional MetS factors), a similar prevalence rate for MetS (5.9%, 26/440) was observed. The overall prevalence rate for diabetes was 0.8% (4/488). The proportion of subjects with at least one pre-existing MetS risk factor was 58% (281/488), with a similar rate between male (57%) and female subjects (59%).

Table 1 shows the differential gender prevalence of metabolic abnormalities in these first-episode, partially drug-naive patients with schizophrenia. There was a statistically significantly higher prevalence of elevated triglyceride levels and blood pressure in the male cohort compared to the female group. In contrast, the prevalence for abdominal obesity and low HDL levels was higher in the female cohort.

MetS prevalence was similar for antipsychotic-naïve (5.6%, 9/160) vs. non-naïve first-episode patients (6.1%, 20/328) in this study. The overall rates for individual MetS criteria in drug-naïve subjects (n = 160) were (%): WC 5; triglycerides 14; HDL 28; glucose 6; blood pressure 31. Differences between antipsychotic-naïve and non-naïve subjects were non-significant for all MetS risk factors (all \( p > 0.05 \)), except for blood pressure elevation (in drug-naïve subjects 31% or 50/160, vs. non-naïve subjects 21% or 68/328, \( p = 0.02 \)).

**Treatment effects over the 52-wk treatment period on individual risk factors**

**Body weight**

The ziprasidone group had a significantly smaller increase in BW over a follow-up period of 52 wk compared to all other treatment groups (\( p = 0.004 \), haloperidol (vs. ziprasidone) \( \times \) time interaction term; \( p = 0.004 \) for quetiapine; \( p < 0.001 \) for amisulpride; \( p < 0.001 \) for olanzapine). Figure 1 shows the least squares (LS) mean BW by the mixed model for repeated measures model (MMRM) at baseline and at 13, 26 and 39 wk. The LS mean weight change at individual visits was estimated by visit \( \times \) treatment interaction effect. In the ziprasidone group, the LS mean by MMRM was 65.9 kg at baseline (same in all treatment groups) and 67.8, 67.8, 67.5 and 68.4 kg at 13, 26, 39 and 52 wk, respectively. The amisulpride treated subjects had significantly greater weight gain than the ziprasidone group at 26 wk (\( p < 0.001, t = 3.72, 72.4 \) kg), 39 wk (\( p < 0.001 , t = 4.54, 73.6 \) kg) and 52 wk (\( p < 0.001, t = 3.95, 74.2 \) kg), but not at 13 wk (\( p = 0.081, t = 1.75, 69.5 \) kg). The haloperidol treated subjects had significantly greater weight gain than the ziprasidone group at 26 wk (\( p = 0.023, t = 2.28, 70.9 \) kg), 39 wk (\( p = 0.003, t = 2.94, 72.0 \) kg) and 52 wk (\( p = 0.022, t = 2.29, 72.3 \) kg), but not at 13 wk (\( p = 0.163, t = 1.40, 69.3 \) kg). The quetiapine and the olanzapine groups had significantly greater weight gain than the ziprasidone at all post-treatment visits (\( p < 0.023 \) for all). The LS mean weight for quetiapine and olanzapine was, respectively: 71.2 and 72.5 kg at 13 wk; 72.5 and 75.5 kg at 26 wk; 72.7 and 76.7 kg at 39 wk; 73.0 and 77.1 kg at 52 wk.

The increase in BW from baseline to the 52-wk endpoint (LOCF) in patients treated with haloperidol (LS mean change 5.48 kg, \( t = 2.15, p = 0.03 \)) amisulpride (7.17 kg, \( t = 3.72, p < 0.001 \)), olanzapine (10.06 kg, \( t = 5.96, p < 0.001 \)) and quetiapine (6.68 kg, \( t = 3.19, p = 0.002 \)) was significantly greater than that in the ziprasidone group (LS mean change 2.24 (s.e. 1.1) kg, adjusted for drop-out time, baseline and countries in analysis of covariance (ANCOVA)). There was also no significant treatment \( \times \) drug-naïve status interaction effect on mean weight change (\( p = 0.842, F = 0.35, d.f. = 4, 274 \)).

**Abdominal obesity**

As with weight change, the ziprasidone group showed a smaller increase in mean WC over a follow-up period of 52 wk compared to the haloperidol (haloperidol (vs. ziprasidone) \( \times \) time interaction term, \( p = 0.008 \)) and the other SGAs (all \( p < 0.004 \)), while no differences were found between haloperidol and the other SGAs in terms of the time trend (time \( \times \) treatment interaction: \( p = 0.412 \) for amisulpride vs. haloperidol; \( p = 0.185 \) for olanzapine; \( p = 0.951 \) for quetiapine). Figure 2 shows the LS mean WC by MMRM model at baseline and at 13, 26 and 52 wk. In the ziprasidone group, the LS mean WC by MMRM was 81.3 cm at baseline (same in all treatment groups) and 82.5, 82.1 and 82.7 cm at 13, 26 and 52 wk respectively. The amisulpride-treated subjects had significantly greater WC gain than the ziprasidone group at 26 wk (\( p = 0.006, t = 2.75, 86.4 \) cm), 39 wk (\( p < 0.001, t = 4.43, 88.7 \) cm) and 52 wk (\( p < 0.001, t = 3.59, 88.9 \) cm), but not at 13 wk (\( p = 0.246, t = 1.16, 84.2 \) cm). The haloperidol treated subjects had significantly greater WC gain than the ziprasidone group at 26 wk (\( p = 0.021, t = 2.31, 86.2 \) cm) and 39 wk (\( p = 0.005, t = 2.78, 86.8 \) cm), but not at 13 wk (\( p = 0.163, t = 1.40, 83.6 \) cm) or 52 wk (\( p = 0.081, t = 1.75, 86.3 \) cm). The quetiapine and the olanzapine groups had significantly more WC gain than the ziprasidone group at all post-treatment visits (all \( p < 0.002 \)). The LS mean WC for quetiapine and olanzapine was, respectively, 86.7 and 86.6 cm at 13 wk, 87.8 and 89.9 cm at 26 wk, 87.5 and 90.8 cm at 39 wk and 88.4 and 89.6 cm at 52 wk.
Table 1. Baseline cardiovascular and metabolic syndrome risks

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Drug-naive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (n = 298)</td>
<td>F (n = 200)</td>
</tr>
<tr>
<td>Age (yr; mean ± S.D.)</td>
<td>25.6 ± 5.5</td>
<td>26.5 ± 5.7</td>
</tr>
<tr>
<td>Overweight (BMI 25–29.9)</td>
<td>49/288 (17%)</td>
<td>21/196 (11%)</td>
</tr>
<tr>
<td>Obese (BMI &gt; 30)</td>
<td>7/288 (2.4%)</td>
<td>7/196 (3.6%)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l) Mean ± S.D.</td>
<td>4.42 ± 1.07</td>
<td>4.53 ± 1.10</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.3 (3.7, 5.0)</td>
<td>4.4 (3.8, 5.1)</td>
</tr>
<tr>
<td>Insulin (mU/l) Mean ± S.D.</td>
<td>10.2 ± 14.5</td>
<td>10.0 ± 7.2</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>7 (4, 10)</td>
<td>8 (5, 14)</td>
</tr>
<tr>
<td>HOMA-IR Mean ± S.D.</td>
<td>0.33 ± 0.61</td>
<td>0.30 ± 0.24</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.21 (0.13, 0.32)</td>
<td>0.22 (0.15, 0.40)</td>
</tr>
<tr>
<td>Hypertension Mean ± S.D.</td>
<td>32/291 (11%)</td>
<td>8/197 (4.1%)</td>
</tr>
<tr>
<td>BP (≥ 140/90 mm Hg)</td>
<td>3/288 (1%)</td>
<td>1/193 (0.5%)</td>
</tr>
<tr>
<td>MetS, metabolic syndrome</td>
<td>17/290 (5.9%)</td>
<td>12/193 (6.2%)</td>
</tr>
<tr>
<td>WC (M &gt; 102 cm, F &gt; 88 cm)</td>
<td>10/258 (4%)</td>
<td>26/182 (14%)</td>
</tr>
<tr>
<td>TG (&gt;150 mg/dl or &gt; 1.695 mmol/l)</td>
<td>62/291 (21%)</td>
<td>24/195 (12%)</td>
</tr>
<tr>
<td>HDL (M &lt; 40 mg/dl or &lt; 1.036 mmol/l, F &lt; 50 mg/dl or &lt; 1.295 mmol/l)</td>
<td>65/282 (23%)</td>
<td>70/192 (36%)</td>
</tr>
<tr>
<td>BP (≥ 130/85 mm Hg)</td>
<td>83/291 (29%)</td>
<td>35/197 (18%)</td>
</tr>
<tr>
<td>Glucose (&gt;100 mg/dl or &gt; 5.55 mmol/l)</td>
<td>23/288 (8.0%)</td>
<td>12/193 (6.2%)</td>
</tr>
<tr>
<td>MetS ATP-III-A (AHA): if any of 5 criteria are met</td>
<td>13/258 (5.0%)</td>
<td>13/182 (7.5%)</td>
</tr>
<tr>
<td>WC (M &gt; 94 cm, F &gt; 80 cm)</td>
<td>35/258 (14%)</td>
<td>48/182 (26%)</td>
</tr>
<tr>
<td>TG (&gt;150 mg/dl or &gt; 1.695 mmol/l)</td>
<td>62/291 (21%)</td>
<td>24/195 (12%)</td>
</tr>
<tr>
<td>HDL (M &lt; 40 mg/dl or &lt; 1.036 mmol/l, F &lt; 50 mg/dl or &lt; 1.295 mmol/l)</td>
<td>65/282 (23%)</td>
<td>70/192 (36%)</td>
</tr>
<tr>
<td>BP (≥ 130/85 mm Hg)</td>
<td>83/291 (29%)</td>
<td>35/197 (18%)</td>
</tr>
<tr>
<td>Glucose (&gt;100 mg/dl or &gt; 5.55 mmol/l)</td>
<td>23/288 (8.0%)</td>
<td>12/193 (6.2%)</td>
</tr>
<tr>
<td>None of the ATP risk factors</td>
<td>102/244 (42%)</td>
<td>73/178 (41%)</td>
</tr>
<tr>
<td>Any of the 1 ATP risk factors</td>
<td>110/295 (37%)</td>
<td>78/200 (39%)</td>
</tr>
<tr>
<td>Any of the 2 ATP risk factors</td>
<td>40/293 (14%)</td>
<td>26/196 (13%)</td>
</tr>
<tr>
<td>Any of the 3 ATP risk factors</td>
<td>15/290 (5%)</td>
<td>11/193 (6%)</td>
</tr>
<tr>
<td>Any of the 4 ATP risk factors</td>
<td>2/283 (0.7%)</td>
<td>1/190 (0.5%)</td>
</tr>
<tr>
<td>Any of the 5 ATP risk factors</td>
<td>0/244 (0%)</td>
<td>0/178 (0%)</td>
</tr>
</tbody>
</table>

M, Male; F, female; IQR, inter-quartile range; BMI, body mass index; WC, waist circumference; TG, triglycerides; BP, blood pressure; MetS, metabolic syndrome; ATP, National Cholesterol Education Program’s Adult Treatment Panel; AHA, American Heart Association; HOMA-IR, homeostatic model assessment, insulin resistance; IDF, International Diabetes Federation.

*a* Denominator for three of the five MetS risk factors: number of subjects with a maximum of two missing risk factor values.

*b* Denominator for proportion of subjects with none of the five MetS risk factors: number of subjects with no missing data in all five MetS risk factors.

*c* Denominator for proportion of subjects with any one of the MetS risk factors: total number of subjects.

For categorical outcomes, analysis was based on Fisher’s exact test.

Diabetes was considered present in the study if the participant was under treatment with insulin or oral hypoglycaemic agents, or if fasting blood glucose exceeded 126 mg/dl or 6.993 mmol/l at the screening baseline.

Increase in WC (cm) from baseline to 52-wk end-point (LOCF) was observed in patients treated with haloperidol (LS mean change 4.3 cm, t = 1.94, p = 0.054), amisulpride (6.02 cm, t = 3.40, p < 0.001), olanzapine (7.95 cm, t = 4.91, p < 0.001), quetiapine (7.25 cm, t = 3.95, p < 0.001) and was significantly greater than that in the ziprasidone group (LS mean change 1.14 (S.E. 1.13) cm, ANCOVA). There was also no significant treatment and drug-naive status interaction effect on mean WC change (p = 0.886, F = 0.29, d.f. = 4, 264).
Insulin resistance HOMA-IR

Elevated HOMA-IR from baseline to 52-wk end-point (LOCF) was observed in amisulpride (median change 0.77 s.e. 0.23, ANCOVA) which was significantly higher than quetiapine (median change 0.28, s.e. 0.19, p = 0.015) or ziprasidone (median change 0.03 s.e. 0.18, p = 0.011) and a significant trend for haloperidol (median change −0.10 s.e. 0.33, p = 0.086), but not olanzapine (median change 0.68 s.e. 0.30, p = 0.353). Elevated HOMA-IR was also observed in olanzapine which showed a significant trend increase when comparing with quetiapine (p < 0.100) or ziprasidone (p = 0.094).

Hyperglycaemia

Worsening in glucose levels was defined as a shift from a normal baseline to hyperglycaemia (≥100 mg/dl or ≥5.55 mmol/l); an improvement was defined as a shift from hyperglycaemia at baseline to a normal state. The distributions of subjects who worsened or improved over a follow-up period of 52 wk with respect to glycaemia are shown in Table 2. Treatment differences were not statistically significant. However, four (0.82%) subjects had fasting glucose at diabetic level (≥126 mg/dl or ≥6.993 mmol/l) during the 52-wk follow-up period: three of these subjects (two on olanzapine and one on amisulpride) switched from normal level (≤99 mg/dl or ≤5.494 mmol/l) and another subject on amisulpride switched from impaired fasting glucose (104 mg/dl or 5.772 mmol/l) to diabetic level.

Hypertriglyceridemia

A worsening in triglyceride levels was defined as a shift from a normal baseline to elevated triglycerides (≥150 mg/dl or ≥1.695 mmol/l). An improvement in triglycerides level was defined as a shift from an elevated to a normal level. The distributions of subjects who had worsened or improved triglyceride levels over a follow-up period of 52 wk are shown in Table 2. Treatment differences were not statistically significant.

Hypercholesterolaemia

Worsening in total cholesterol levels was defined as a shift from a normal baseline to hypercholesterolaemia (≥200 mg/dl or ≥5.178 mmol/l); an improvement was defined as a shift from hypercholesterolaemia at baseline to a normal state. The distributions of subjects who worsened or improved over a follow-up period of 52 wk with regard to total cholesterol are shown in Table 2. Again, these differences did not reach significance levels.

Suboptimal HDL

The percentage of subjects who showed a reduction in HDL (<40 mg/dl or <1.036 mmol/l for men, <50 mg/dl or <1.295 mmol/l for women) over a follow-up period of 52 wk from normal baseline was higher in the olanzapine (24.1%, t = 2.39, p = 0.017, vs. haloperidol) and amisulpride (22.5%, t = 2.05, p = 0.040, vs. haloperidol) groups, but was lower in the quetiapine (10.6%), haloperidol (10.9%) and ziprasidone (15%) groups. The rates of improvement in HDL level (from undesirable, low HDL levels at baseline) were similar among all groups (ranging from 8.4% for amisulpride to 12.8% for ziprasidone).

Discussion

In this open-label, randomized 52-wk trial of five commonly-used antipsychotics (amisulpride, haloperidol, olanzapine, quetiapine and ziprasidone), we found that 5.9% of subjects met the criteria for MetS and 58% of subjects had one or more individual MetS risk factors at
baseline. A similar rate of MetS was observed in antipsychotic-naive patients (5.6%, 9/160) as in patients with a brief pre-exposure to antipsychotics (6.1%, 20/328). Our findings suggest that the baseline prevalence rate of MetS in the EUFEST patients appears to be no higher than that in a general population of similar age.

The baseline prevalence of overweight and obesity (BMI >25) among EUFEST subjects was considerable (19% for male; 14% for female; Table 1). In EUFEST, female subjects had a numerically higher MetS prevalence ratio than their male counterparts by a small and non-significant margin (6.2% vs. 5.8% using NCEP-ATP-III criteria). Among the five antipsychotics studied over the 52-wk trial period, elevations of insulin resistance as estimated by HOMA-IR was significantly higher in the amisulpride group than the quetiapine and ziprasidone groups, with a trend towards significance when comparing with haloperidol. Treatment difference in HOMA-IR level between amisulpride and olanzapine was non-significant. Amisulpride and olanzapine led to a non-significantly larger increase in triglyceride levels (from normal to abnormal). The proportions of subjects who showed a reduction in HDL were also highest in these groups, with significant differences when compared to haloperidol. All treatment groups showed a mean increase in glucose levels, with those shifting from normal baseline to hyperglycaemia (>100 mg/dl or >5.55 mmol/l) ranging from 21% in the olanzapine group to 10.6% in the haloperidol group.

Our findings are consistent with results of the MetS rate (5.6%, NCEP-ATP-III criteria) and a relatively high prevalence of individual risk factors reported in a chart-review study on a Belgian cohort of first-episode schizophrenia patients (mean age: 21.9 s.d. 3.2 yr; De Hert et al., 2008). In contrast, recent systematic reviews reported 11.3% for MetS in studies of patients who were drug naive or in their first episode (Mitchell et al., 2011, 2012a). A relatively higher rate of 18.3% for MetS, as based on the WHO definition (which requires a hyperinsulinaemic clamp to measure insulin resistance), was also found in a sample of 218 acute psychosis patients aged 18–65 yr who were consecutively admitted to the emergency ward of a Norwegian hospital between March 2004 and February 2009 (Johnsen et al., 2011).

The MetS prevalence rate of 5.9% found in our cohort also parallels large-scale general population surveys. For age groups comparable to our EUFEST patients, de Kroon et al., (2008) found an overall prevalence of MetS of 7.5%, according to NCEP-ATP-IIIA criteria, in their follow-up of 642 young adults aged 19–28 yr from an original Dutch cohort of 2599 subjects. Moreover, our findings are comparable to the 6.7% MetS prevalence rate reported for USA men and women aged 20–29 yr in an analysis of 8814 adults aged >20 yr from the NHANES-III (1988–1994) survey (Ford et al., 2002). More recent data show that prevalence of MetS had increased significantly from NHANES-III to NHANES 1999–2006 among young women aged 20–39 yr (p = 0.010), but the increase was not significant in men aged 20–39 yr (p = 0.08; Mozumdar and Liguori, 2011). Our results are also compatible with those from the data from an epidemiological study of the insulin resistance syndrome (DESIR) study involving 2109 French males and 2184 females aged 30–64 yr (Balkau et al., 2003). DESIR found an overall MetS prevalence rate of 20% for men and 7% for women (using the NCEP-ATP-III criteria) not on any antidiabetic, hypertensive or lipid lowering medications. Overall, these data indicate that the MetS prevalence rate observed in the first-episode patients in EUFEST is comparable to the general population of similar age.

Despite the fact that baseline MetS prevalence in our patients was comparable to that reported in the general population, serious underlying individual risk factors nevertheless existed. EUFEST findings showed that 58% (281/488) had at least one pre-existing MetS risk factor. This compares to surveys showing that in the USA, about half the adolescents aged 12–19 yr have at least one of the five components of metabolic disorders (Johnson et al.,
and that >54% of young adults (male: aged 20–35 yr; female: aged 20–45 yr) have >1 coronary heart disease (CHD) risk factors (hypertension, obesity, smoking and family history of CHD; Johnson et al., 2009). Further, a Centers for Disease Control and Prevention report estimated that in the USA about 45% of all adults aged >20 yr have hypercholesterolaemia, hypertension or diabetes, 13% have two of the three conditions and 3% have all three conditions (Kulina et al., 2010). Prevalence rates for similar individual risk factors were generally comparable to corresponding estimates by WHO for Europe as a whole and for high-income European countries in particular, except for high blood pressure (higher WHO estimate for Europe as a whole) and overweight or obesity [higher estimate for high-income America, i.e. USA and Canada; (WHO, 2009)]. Geographical diversity in eating behaviour and lifestyle between the USA and Europe needs to be taken into account when comparing these figures.

The tendency for some antipsychotic agents to induce excessive weight gain and expand WC increases the risk for metabolic and related medical disorders. In our study, four (0.8%) newly diagnosed cases of diabetes (two on olanzapine and two on amisulpride) occurred during the 52-wk treatment period. Of these four patients, two were females and both had a substantial increase in abdominal obesity as assessed by an increase in WC (from 60 cm to 90 cm and from 64 cm to 76 cm, respectively). This overall rate is consistent with the 0.65% annual incidence rate of type 2 diabetes observed in the Danish follow-up study of antipsychotic-naive patients with schizophrenia (Nielsen et al., 2010). This Danish study followed 7139 antipsychotic-naive patients with schizophrenia for a mean 6.6 yr (47 297 patient yr) between January 1997 and December 2004. Besides general diabetes risk factors such as older age, hypertension and dyslipidaemia, they also found increased risks of diabetes were associated with ‘initial’ and current treatment with mid-potency first-generation antipsychotics and the SGAs, olanzapine and clozapine (Nielsen et al., 2010). The investigators noted that current treatment with the SGA aripiprazole reduced the risk of diabetes. There was no increased risk of diabetes after patients discontinued olanzapine or mid-potency first-generation antipsychotics compared to patients not treated with the drugs at any time.

The importance of WC change as a useful indicator for metabolic risks in schizophrenia cannot be over-emphasized. Abdominal or visceral fat deposition represents a much greater danger for the future development of diabetes and other insulin-related disorders than other phenotypes of obesity, such as fat deposit on the hips and buttocks. Monitoring change in WC and/or the waist:hip ratio has proven to be a simpler, more reliable and significant predictor of metabolic disorders and conversion to type 2 diabetes mellitus than calculated BMI (Stamler et al., 2000; Despres and Lemieux 2006; Mattsson et al., 2008). Underlying the growing importance of WC change is its elevation to be the only mandatory risk factor measure in the IDF definition of MetS (Wagenknecht et al., 2003).

Despite the wealth of data available, routine testing and monitoring by psychiatric care providers of patients taking antipsychotic prescriptions for metabolic and other adverse effects remains inadequate and relatively unchanged (Kurzthaler and Fleischhacker, 2001; Tschoner et al., 2007; Ervin, 2009; Mitchell et al., 2012b). One major obstacle is the lack of access to costly, complex blood and glucose tests at the typical psychiatric clinics or mental healthcare settings. Promoting easy and ready-to-undertake waist measurement to the psychiatric healthcare providers may be an inexpensive, convenient way to mitigate the lack of awareness and ease the routine monitoring of weight/metabolic risks in this at-risk population.

To our best knowledge, EUFEST represents the largest longer-term study of first-episode schizophrenia patients, with little or no prior exposure to antipsychotic treatment, available to date. Despite limitations such as multiple definitions, technical difficulties in the consistent measurement of some of the parameters and controversies over its clinical significance, there is considerable agreement that the cluster of lipid and non-lipid risk factors commonly referred to as ‘metabolic syndrome’ is a major contributor to the risk of developing cardiovascular disease and type 2 diabetes (Eckel et al., 2005; Reaven, 2005; Kahn, 2008). Our analysis has several notable limitations. The prevalence rate of MetS was estimated using baseline data from this randomized, comparative, naturalistic schizophrenia treatment trial, which might be less representative than large, population-based cohort studies. The lack of a matched, healthy control group did not allow direct comparison of the prevalence rates with those unexposed to antipsychotics. Our literature review, however, shows EUFEST results are consistent with those previously reported for specific or general European populations. EUFEST was not specifically designed to evaluate MetS and specific metabolic risk factors. Because blood pressure was assessed only at the baseline visit, drug-specific changes in the individual risk factors were reported instead of the rates of MetS.

There were differential drop-out rates in the treatment arms, which may have had an impact on the occurrence of various metabolic adverse events. For instance, patients on haloperidol, who on average dropped out much earlier, may not have had the same exposure to develop the weight gain and other side-effects common among those on olanzapine for the full study period. However, missing data may cause bias in mixed effects modelling of longitudinal profiles only if the probability of missing data is dependent on the value of missing items (non-random or informative). Although the EUFEST naturalistic design helped avoid potential
confounding effects due to prior antipsychotic medications and the more rigid inclusion and exclusion criteria typical of placebo-controlled randomized controlled trials, selection bias can never be entirely ruled out. Similarly, the intervals between measurements were protracted and complete laboratory parameters were collected only at baseline and at the 26- and 52-wk endpoints. Findings other than those on baseline risks may therefore be less robust.

In summary, our findings strengthen previous observations on the prevalence of baseline metabolic abnormalities and on the differential effects antipsychotics can have on weight and metabolic risks in first-episode schizophrenia patients. The MetS rate observed in the first-episode patients in EUFEST appears to be no higher than that in a general population of similar age (Stamler et al., 2000; Despres and Lemieux, 2006; Mattsson et al., 2008; Mitchell et al., 2011).

These results suggest that most of the elevated metabolic risks in chronic schizophrenia patients may be attributed to the side-effects of antipsychotic pharmacotherapy and/or the illness itself. Our findings underscore the importance of enhanced monitoring of metabolic risk factors and customizing the choice of antipsychotic therapy accordingly.

Acknowledgements

EUFEST was funded by the European Group for Research in Schizophrenia (EGRIS) with grants from AstraZeneca, Pfizer and Sanofi-Aventis. Data Power, Inc. provided statistical support. Pfizer provided programming and medical writing support for this report, but the final approval of content was exclusively retained by the investigators and interpreted collectively by all of the authors. The decision to submit the paper for publication was also made by all co-authors.

Statement of Interest

W. W. F. receives research grants from Otsuka, Pfizer, Janssen, Alkermes, Eli Lilly; consulting honoraria from Lundbeck, Roche, BMS, Otsuka, Janssen, Pfizer, UnitedBioSource, MedAvante, Sunovion, Merck; speaker honoraria from Lundbeck, Sunovion, Janssen, Eli Lilly, Otsuka, Astra Zeneca; and owns MedAvante stocks.

C. O. S. was a paid consultant to Pfizer in connection with the development of this manuscript and has served as a consultant to Pfizer, Dainippon Sumitomo Pharma/Sepacor (now Sunovion Pharmaceuticals, Inc.), Memory Pharmaceutical/Roche Laboratories and Wyeth over the past 3 yr. O. N. K. and E. P. are full-time employees of Pfizer, Inc. RSK has received grants, honoraria for education programmes and/or served as consultant for AstraZeneca, BMS, Eli Lilly, Janssen-Cilag, Pfizer and Sanofi-Aventis.

References


