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Original article

A four-year naturalistic prospective study of cardiometabolic disease in antipsychotic-treated patients

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ABSTRACT

The relationship between antipsychotic use and cardiovascular morbidity and mortality is controversial. There is a lack of long-term prospective studies investigating changes in cardiometabolic risk in patients treated with antipsychotic drugs. We report data from a 4-year prospective study. Patients (89) underwent detailed metabolic and cardiovascular risk assessment at 4-years which included anthropometric assessment, blood pressure, lipid profile, and an oral glucose tolerance test. We used the homeostatic model assessment to determine insulin resistance, and calculated 10-year cardiovascular risk scores. Mean age of subjects was 44.7 (±11.5) years, and 52% were male. The prevalence of type 2 diabetes was 8%, and 38.4% fulfilled diagnostic criteria for the metabolic syndrome. With the exception of increased central adiposity over the 4-year follow-up period ($p < 0.001$), other cardiometabolic parameters were generally unchanged. There was a high prevalence of dyslipidaemia, but only 16.9% were prescribed lipid-lowering treatment. Commencing lipid-lowering therapy was associated with a reduction in cardiovascular risk score (OR 7.9, 95% CI = 1.3 to 48.7; $p = 0.02$). Patients established on longer-term antipsychotic treatment show less dramatic metabolic changes than those occurring in the early stages of treatment, but have a high burden of cardiovascular risk. Lipid-lowering therapy is associated with a significant reduction in cardiovascular risk.

1. Introduction

Individuals with severe mental illnesses such as schizophrenia and bipolar disorder have an increased risk of death from coronary artery disease and stroke [20]. The introduction of second-generation (or atypical) antipsychotic drugs has been associated with increased mortality in patients with schizophrenia as a result of cardiovascular disease [25], although a recent population-based cohort study from Finland reported that long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use [24].

Although the data regarding mortality are controversial, the advent of the atypical antipsychotic drugs has been accompanied by a burgeoning literature reporting an increased prevalence of cardiovascular risk factors in patients prescribed these drugs [19]. However, it is not known how the early metabolic perturbations following commencement of antipsychotic treatment translate into longer-term cardiovascular risk and mortality. Furthermore, it has been consistently reported that monitoring of cardiovascular risk factors in psychiatric patients is poor [6,17,18], and interventions to reduce cardiovascular risk are inadequate.

In 2004, we established a cohort of antipsychotic-treated patients with the intention of prospectively studying these patients to investigate changes in cardiometabolic risk over time. We have previously reported changes in cardiovascular risk over an 18-month period [17], and in the current study, we report the 4-year follow-up data.

2. Subjects and methods

2.1. Subjects

One hundred and six patients, irrespective of diagnosis, were recruited from psychiatric out-patient clinics in the North East of England. The only entry criteria were that the patient had been prescribed an antipsychotic drug (typical, atypical or combination) and was clinically stable. Patients with eating disorders, those actively misusing illicit substances or alcohol, and those with serious underlying physical co-morbidity (i.e. malignant disease or end-stage organ failure) were excluded. All subjects recruited at baseline were invited to participate in this phase of the prospective study. Subjects gave written informed consent to participate, and the study was approved by the Newcastle upon Tyne Local Research Ethics Committee.

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2.2. Procedures

Participants were given verbal and written instructions to fast from midnight on the day of assessment, and fasting status was confirmed by a member of the research team. All assessments were performed between 8.30am and 10.00am on the study day. Demographic and illness characteristics were recorded, together with family history of cardiovascular disease and type 2 diabetes mellitus. Current medication and dosage was recorded, and confirmed, where necessary, by reference to case notes and general practitioner records.

Height, weight, and waist and hip circumference were recorded using standard anatomical landmarks. Blood pressure was measured using an automated sphygmomanometer, and the mean of three readings taken at rest was used. A 12-lead ECG was recorded in order to determine the presence of left ventricular hypertrophy. A venous blood sample was taken for analysis of plasma glucose, insulin and lipid profile. HbA_{1c} was also measured. Insulin was measured by ELISA. The homeostatic model assessment [15] was used to calculate pancreatic β-cell function (HOMA-β), insulin sensitivity (HOMA-S) and insulin resistance (HOMA-IR). An oral glucose tolerance test was performed in which the patient was given 75 g of glucose in 300 ml of water which was consumed over a 5 minute period. A blood test for plasma glucose was taken 2 hours later. The presence of the metabolic syndrome was determined using the International Diabetes Federation criteria [4]. Ten-year cardiovascular disease risk scores were calculated based on the Framingham equation.

2.3. Statistical analysis

Data were analysed using the Statistical package for the Social Sciences, version 17.0. Serum triglycerides and Framingham 10-year risk scores were not normally distributed, and these variables were therefore log transformed. Owing to the number of metabolic parameters measured and the risk of type 1 error, we first conducted a repeated measures multivariate analysis of variance (MANOVA) to test for an overall significant effect of time on continuous metabolic parameters. Paired *t*-tests or McNemar tests were then used to compare demographic and clinical parameters between individual subjects at baseline and 4 years, and baseline and 18 months. Analysis of variance (ANOVA) was used to examine the interaction between type of antipsychotic drug treatment (i.e. typical or atypical), or no drug treatment, on changes in metabolic parameters. Regression models were used to investigate predictors of change in metabolic parameters after controlling for potentially confounding variables. All reported p values are two-tailed, and statistical significance is defined as $p < 0.05$.

3. Results

3.1. Characteristics of participants

Of the original 106 participants in the baseline study, 89 (84%) consented to participate in the 4-year follow-up. All patients were receiving community psychiatric care and were considered to be clinically stable at the time of assessment. Follow-up was not possible for 17 (16%) patients for the following reasons: refusal to participate ($n = 9$); no response to invitation ($n = 4$); moved to another area ($n = 3$); too ill to participate ($n = 1$); deceased ($n = 1$). Characteristics of the participants are given in Table 1.

3.2. Medication

Seventy-seven patients (86.5%) were still taking antipsychotic medication at the four year follow up, and of these, 55 (72.4%) were taking the same antipsychotic regimen as prescribed at baseline assessment. Of those taking atypical drugs ($n = 64$) the following antipsychotic drugs were prescribed: olanzapine ($n = 27$, 42.1%), quetiapine ($n = 13$, 20.3%), clozapine ($n = 10$, 15.6%) risperidone ($n = 8$, 12.5%), amisulpride ($n = 4$, 6.2%) and aripiprazole ($n = 2$, 3.3%) Of the patients prescribed typical agents ($n = 19$), the following drugs were prescribed: flupenthixol ($n = 6$, 32%), sulpiride ($n = 3$, 15.8%), zuclopenthixol ($n = 2$, 10.5%), fluphenazine ($n = 2$, 10.5%), trifluoperazine ($n = 2$, 10.5%), chlorpromazine ($n = 1$, 5.3%), haloperidol ($n = 1$, 5.2%), pipothiazine ($n = 1$, 5.2%) and promazine ($n = 1$, 5.2%).

Table 1
Characteristics of 89 patients who were available for follow-up at 4 years.

	$n = 89$
Age, years (mean ± SD)	44.7 (11.5)
Gender, m:f, *n* (%)	46:43 (52:48)
Ethnicity, white British, *n* (%)	87 (97.8)
Family history type 2 diabetes, *n* (%)	26 (29.2)
Family history CVD, *n* (%)	52 (58.4)
Diagnosis	
Schizophrenia, *n* (%)	32 (36.0)
Schizo-affective disorder, *n* (%)	8 (9.0)
Bipolar disorder, *n* (%)	30 (33.7)
Depressive disorders, *n* (%)	19 (21.3)
Time since baseline study, months (mean ± SD)	48.1 (6.7)
Duration of illness, months (mean ± SD)	216 (152.3)
Antipsychotic medication	
Typical, *n* (%)	17 (19.1)
Atypical, *n* (%)	59 (66.3)
Combination, *n* (%)	13 (14.6)
Antidepressant medication, *n* (%)	45 (50.6)
Mood stabiliser, *n* (%)	30 (33.7)

3.3. Cardiometabolic parameters

Cardiometabolic parameters at baseline, 18-month follow-up and 4-year follow-up are given in Table 2. At 4-year follow-up, 8% ($n = 7$) patients had diabetes and 39% of patients fulfilled criteria for the metabolic syndrome. The number of patients smoking significantly reduced from 50.6% at baseline to 39.3% at four years follow-up. There was a highly significant overall main effect of time on changes in cardiometabolic parameters ($MANOVA_{\text{baseline to 4yrs}}$; $F = 3.71$, $df = 14,59$, $p < 0.001$). Mean waist circumference and waist:hip ratio were significantly increased over the 4-year follow-up period; after controlling for age, gender, smoking status and antipsychotic, antidepressant and mood stabiliser medication, lower baseline waist circumference was a highly significant independent predictor of increased waist circumference over time ($\beta = -0.40$, $p = 0.001$). HbA_{1c} and HDL cholesterol were also significantly increased at 4-year follow-up compared with baseline. The number of subjects fulfilling metabolic syndrome criteria for central obesity and low HDL levels also increased over four years. Other metabolic parameters (BMI, measures of insulin resistance, total cholesterol, LDL cholesterol, and triglycerides) were not significantly different from baseline. As blood pressure readings were not available at the baseline assessment (and therefore the prevalence of the metabolic syndrome and 10-year cardiovascular risk scores could not be calculated), these parameters were compared between the 18-month and 4-year follow-up periods. There was no significant change in the prevalence of the metabolic syndrome or Framingham 10-year cardiovascular risk score between these two time points.

3.4. Effect of discontinuing antipsychotic treatment

Tables 3 and 4 show the mean changes in metabolic parameters over 4 years in those patients who have continued, and those who have discontinued antipsychotic treatment. BMI, waist circumfer-