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ARTICLE

Course of weight gain and metabolic abnormalities in first treated episode of psychosis: the first year is a critical period for development of cardiovascular risk factors

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Abstract

Data on the long-term metabolic side-effects associated with antipsychotics are scarce. Prospective longitudinal studies in medication-naive patients with a first episode of psychosis are a valuable source of information as they provide an assessment prior to the antipsychotic exposure and minimize the effect of potential confounding factors. The aim of this study was to assess the course of weight gain and the incidence of metabolic abnormalities during the first 3 yr of antipsychotic treatment. Data were collected from a cohort of 170 first-episode psychosis patients. They were randomly assigned to haloperidol (32%); olanzapine (32%) and risperidone (36%). The dose used was flexible. The initial antipsychotic treatment was changed when required, based on clinical response and tolerability. The results showed that the mean weight gain at 3 yr was 12.1 kg (S.D. = 10.7). It appeared to increase rapidly during the first year (85% of the total mean weight gain) and then stabilized gradually over time. Total cholesterol, LDL-cholesterol and triglyceride levels followed a similar trajectory with a significant increase only during the first year. No significant changes were detected in the mean values of glycaemic parameters. Two patients with a family history of diabetes developed diabetes type II. At short-term the factors positively associated with weight gain were lower body mass index, male gender and olanzapine treatment. At long-term, functional status and clinical response were the main predictors. The results of our study indicate that the first year of antipsychotic treatment is a critical period for weight gain and metabolic changes. Identification of weight gain patterns may help to inform studies that aim to prevent or mitigate the metabolic adverse events associated with antipsychotic therapy.

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Introduction

People with schizophrenia and other serious mental illness live up to 25 yr less than the general population (Saha et al., 2007), with cardiovascular disease being the most frequent cause of death (Mackin and McAllister-Williams, 2006). Antipsychotic therapy among other factors (such as smoking, unhealthy lifestyle or reduced access to care) has been reported to account for this excess of mortality (De Hert et al., 2011). However, the attributable cardiovascular mortality risk associated with antipsychotic therapy is difficult to estimate due to the inherent problems in carrying out long-term prospective studies in patients with first-episode psychosis.

Weight gain and metabolic abnormalities are major concerns of antipsychotic therapy in clinical practice. Patients with a first episode of psychosis who have not been previously treated are particularly susceptible to antipsychotic adverse reactions (Tarricone et al., 2010). According to most guidelines and current clinical practice, after a first episode of psychosis, antipsychotic maintenance treatment is recommended for 2 yr, oscillating between a minimum of 1 yr to indefinite duration.

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Unfortunately, the majority of data available regarding weight gain and metabolic adverse reactions are based on short-term clinical trials. There are very few studies with a follow-up of 2 yr or longer (Gentile, 2006; De Hert et al., 2008; Foley and Morley, 2011) and the full magnitude and frequency of these adverse effects are difficult to establish.

Data from retrospective observational studies have shown that patients under long-term antipsychotic treatment have a higher incidence of obesity, diabetes and dyslipidaemia than the general population (Newcomer, 2005; De Hert et al., 2011). It has been suggested that the incidence of metabolic abnormalities might be overestimated. The findings of these studies could be potentially biased if only those patients with a more severe disease have been screened. In addition, these types of research studies rely on the quality of data already collected and they may not have enough information to control for confounding factors (Holt and Peveler, 2006).

The aim of this study was to assess the course of weight gain and metabolic disturbances associated with long-term antipsychotic treatment. A 3-yr follow-up prospective cohort study was conducted in a medication-naive first-episode psychosis population. We have also explored the predictive value of clinical factors on weight gain.

Method

The study was conducted in the outpatient and inpatient psychiatric services of Marques de Valdecilla University Hospital, Spain. The hospital is a reference centre of a catchment area population of 555 000 people and provides the only psychiatric ward and 24 h emergency care for the whole province. A more detailed description of the study population has been previously reported (Pelayo-Terán et al., 2008). The study protocol was approved by the ethics committee of the Marques de Valdecilla University Hospital.

Study design

Patients recruited into this study were drawn from a consecutive sample of psychotic patients enrolled in our first-episode psychosis programme from February 2001 to February 2005. Patients had to meet the following criteria: (1) age 15–60 yr; (2) living in the catchment area; (3) experiencing their first episode of psychosis; (4) never treated with antipsychotic medication; (5) meeting DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia or schizoaffective disorder; and (6) they understood the nature of the study and signed an informed consent document. Patients were excluded for any of the following reasons: (1) meeting DSM-IV criteria for drug dependence; (2) meeting DSM-IV criteria for mental retardation; and (3) having a serious medical illness. The diagnoses were confirmed according to the DSM-IV criteria, using the Structured Clinical Interview for DSM-IV (SCID-I) by an expert psychiatrist after 6 mth from the initial contact.

At inclusion patients were randomly assigned to receive haloperidol, olanzapine or risperidone. The dose was flexible, based on response and tolerability. Those patients who did not respond after 6 wk or who had significant drug adverse reactions were changed to a different antipsychotic. The lowest effective dose was sought in maintenance treatment.

Certain concomitant medications (lormetazepam and clonazepam) were permitted for the management of agitation, anxiety and/or insomnia. Only if clinically significant extrapyramidal signs occurred, anticholinergic medication was allowed (biperiden up to 8 mg/day). Antidepressants (sertraline) and mood stabilizers (lithium) were permitted if clinically needed. Advice on diet, exercise and lifestyle was given to all patients.

Laboratory assessments

Fasting venous blood samples were collected between 08:00 and 10:00 at baseline, 3 mth and yearly thereafter for 3 yr.

All determinations were performed in our hospital, including both biochemical and endocrinology analysis. Glucose, total cholesterol, HDL cholesterol, and triglycerides were measured by automated methods on a Technicon Dax (Technicon Instruments Corp, USA), using the reagents supplied by Boehringer-Mannheim (Germany). Low-density lipoprotein (LDL) cholesterol was determined by the Friedewald et al., calculation (Friedewald et al., 1972): LDL = total cholesterol – (HDL + [triglycerides/5]).

In addition, a complete blood count and liver function tests based on standard haematological and clinical chemistry values were performed at each visit (data not shown).

Insulin levels were measured by an immunoradiometric assay (IRMA) (Immunotech, Beckman Coulter Company, Czech Republic) with an average interassay coefficient of variation (CV) of 3.3% and intraassay CV of 2.8%. The sensitivity of method was 0.5 μU/ml. Values for normal weight subjects are 2.1–22 μU/ml. This assay does not show any cross-reactivity with human proinsulin and C-peptide.

Homeostasis model assessment (HOMA) was used to assess insulin resistance (IR). The HOMA index was calculated by means of a previously described formula (Matthews et al., 1985): HOMA = [fasting insulin (μU/ml) × fasting glucose (mmol/l)]/22.5. In addition, as proposed by McLaughlin et al. (2005), we calculated the triglyceride/HDL cholesterol (TG/HDL cholesterol) ratio as a predictor of insulin resistance using the cut-point of 3.5 described by them as optimal.

Serum leptin concentrations were measured by specific radioimmunoassay using a commercial kit (Linco Research, USA). The detection limits was 0.5 ng/ml, the

intra-assay CV was 4.5% and the interassay CV was 5.2%. This assay does not show any cross-reactivity with insulin, proinsulin, C peptide, glucagon or insulin-like growth factor I. Values in subjects with normal body mass index (BMI) were <10 ng/ml for men and <20 ng/ml for women.

Clinical assessments

The presence of positive and negative psychotic symptoms was assessed by the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981), respectively. Symptomatic response for positive or negative symptoms was defined as a reduction of at least 40% of the total SANS or SAPS score from baseline and a total SANS or SAPS score $\leqslant 8$ and individual items scoring <3. If symptoms were present, they were only mild and they did not interfere with daily functioning.

Functional status was determined by the Spanish version of the Disability Assessment Scale (DAS) (Mana and Giron, 1998) at baseline, 1 yr and 3 yr follow-up. A psychiatrist and a social worker assessed the patient and their relatives independently. A consensus reach by both on global functioning was used to classify the participants into two subgroups: patients with 'good global functioning' (scored=0=no disability) and patients with 'functional deficits' (scored from 1=minimal disability to 5=extreme disability).

Statistical analyses

To evaluate the changes over time of weight, BMI, lipid and glycaemic measurements, repeated-measures analyses of variance (ANOVA) followed by *post-hoc* Bonferroni tests were used. The level of statistical significance for all tests was set *a priori* at $p<0.05$.

Backwards step-wise linear regression analyses were conducted to assess the association between antipsychotic-induced weight gain and clinical factors. Candidate variables included at the initial stage of the analysis were BMI at baseline, age, sex, socioeconomic level (low *vs.* middle-high), initially assigned treatment (haloperidol, olanzapine or risperidone), duration of untreated psychosis (log-transformed), hospitalization after the first episode of psychosis, positive and negative psychotic symptoms and social functioning (deficit *vs.* non-deficit). In the preliminary analyses we also included smoking status (smoker *vs.* non-smoker) and diagnosis (schizophrenia/schizophreniform *vs.* other diagnosis) but they were omitted in the final models since they were found not to be significant. The analyses were conducted at 3 mth, 1 yr and 3 yr follow-up.

Finally, the McNemar test for repeated measures was used to compare the number of patients with high levels of lipid and glycaemic values (according to the reference values of our laboratory) at baseline and after 3 yr of antipsychotic treatment.

All statistical analysis were performed with the SPSS software package for Windows (version 16.0).

Results

Characteristics of the cohort

A detailed description of the clinical and sociodemographic characteristics of the study population has been previously reported (Crespo-Facorro et al., 2006). A total of 174 patients enrolled in the first episode psychosis programme of Cantabria were included in this clinical trial. Data on the main metabolic variables were available in 170 participants at baseline and in 135 of them at 3 yr (80% of the initial sample). The main reasons for discontinuation were: patient's decision 13% ($n=23$); moving to another city 4% ($n=7$); suicide ($n=1$); prison ($n=1$); and, moving to long-term psychiatric facilities ($n=3$).

The patients had a mean age of 27.3 (S.D.=7.8), 61% were male and most of them were white Caucasian (97%). At 6-mth follow-up, 62% had a diagnosis of schizophrenia, 2% schizoaffective, 23% schizophreniform, 5% brief psychotic episode and 8% unspecified psychotic disorder. Sixty per cent belonged to a low—middle socioeconomic status and 84% lived with family.

At baseline the patients were randomly assigned to receive haloperidol (32%), olanzapine (32%) or risperidone (36%). At 1 yr, 67% of the patients who completed the follow-up continued with the same treatment, at 2 yr 53% and at 3 yr the number decreased to 43%. The mean time to discontinuation was 15.4 mth (95% confidence interval (CI), 11.8–18.8) for haloperidol, 23.8 mth (95% CI, 20.1–27.4) for olanzapine and 20.7 mth (95% CI, 17.2–24) for risperidone. At the end of the follow-up 88% patients were taking second-generation antipsychotics. Prescribed antipsychotics were as follows: 10% haloperidol; 31% olanzapine; 35% risperidone; 7% quetiapine; 6% ziprasidone; 2% amisulpride; 4% clozapine; 3% aripiprazole and 2% other antipsychotics. Results comparing the metabolic side effects of the initial treatments at 3 mth (Perez-Iglesias et al., 2007) and 1 yr have been already published (Perez-Iglesias et al., 2008). No significant differences among treatments were found at 1-yr follow-up.

Course of weight gain, glycaemic and lipid levels

The mean weight gain during the first 3 yr of antipsychotic treatment was 12.1 kg (S.D.=10.7). The majority (78%) of the patients experienced a clinically significant weight gain (>7% of their baseline body weight). The percentage of obese (BMI>30 kg/m^2) patients rose from 4 to 31% at the end of the 3 yr follow-up. The 50th percentile was 10.6 kg.

The maximum increase in weight occurred within the first 12 mth (85% of the mean weight gain and 86% of the mean increase in BMI (see Table 1). The leptin plasma

Table 1. Descriptive data and ANOVA repeated measures analyses of body weight and metabolic changes during the first 3 yr of antipsychotic treatment in a population of first-episode psychosis patients

	Baseline mean (S.D.)	*n*	3 mth mean (S.D.)	*n*	1 yr mean (S.D.)	*n*	2 yr mean (S.D.)	*n*	3 yr mean (S.D.)	*N*	*F** repeated measures	df	*p*	Partial eta squared
Anthropometric changes														
Weight (kg)	67.2 (12.7)	168	72.5 (13.4)	154	77.5 (15.3)	152	77.9 (15.0)	134	79.9 (16.4)	136	58.1	4, 117	<0.001	0.665
BMI (kg/m^2)	23.2 (3.5)	163	25.1 (3.5)	153	26.9 (4.4)	152	27.1 (4.7)	134	27.7 (4.9)	136	58.6	4, 117	<0.001	0.667
Lipid profile														
TC (mg/dl)	173.7 (41.4)	170	188.9 (36.8)	132	196.6 (38.6)	151	192.1 (34.1)	135	189.7 (39.3)	141	13.6	4, 99	<0.001	0.354
LDLc (mg/dl)	109.7 (42.8)	145	119.9 (31.1)	130	123.9 (32.9)	148	122.5 (30.4)	130	119.8 (32.6)	136	8.1	4, 87	<0.001	0.272
HDLc (mg/dl)	50.2 (14.2)	144	49.3 (13.8)	130	49.7 (13.4)	149	46.9 (13.0)	131	47.8 (14.8)	138	4.7	4, 90	0.002	0.174
Triglycerides (mg/dl)	86.7 (40.5)	143	98.7 (51.3)	128	121.8 (99.7)	148	114.9 (55.6)	131	115.8 (73.0)	138	9.4	4, 85	<0.001	0.306
TC/HDLc	3.6 (0.8)	143	4.0 (0.9)	129	4.2 (1.1)	149	4.3 (1.2)	131	4.3 (1.3)	139	17.4	4, 89	<0.001	0.438
Glycaemic parameters														
Glucose (mg/dl)	87.1 (9.8)	170	87.7 (7.7)	133	88.3 (10.3)	149	87.9 (11.1)	135	89.5 (11.4)	140	0.8	4, 97	0.543	0.031
HOMA index	1.7 (1.5)	137	1.9 (1.4)	125	2.2 (2.3)	145	4 (1.8)	124	2.4 (2.2)	126	1.9	4, 75	0.123	0.091
TG/HDLc index	1.9 (1.1)	137	2.2 (1.5)	126	2.8 (2.9)	148	2.7 (1.7)	130	2.8 (2.3)	138	9.9	4, 80	<0.001	0.330
Insulin total (μU/ml)	7.9 (6.8)	139	8.9 (6.1)	125	10.4 (10.0)	148	10.6 (7.2)	126	10.6 (7.2)	128	2.0	4, 79	0.105	0.091
Insulin men	8.0 (7.6)	87	9.5 (6.9)	76	10.6 (11.1)	90	11.1 (7.2)	79	11.2 (7.7)	80	1.7	4, 51	0.174	0.115
Insulin women	7.7 (5.3)	52	7.9 (4.4)	49	10.1 (8.1)	58	9.8 (7.0)	47	9.6 (6.0)	48	1.6	4, 24	0.203	0.212
Hormonal levels														
Leptin total (ng/ml)	7.6 (7.8)	132	10.9 (9.3)	127	13.5 (11.0)	151	13.1 (11.8)	126	12.3 (10.9)	133	24.4	4, 81	<0.001	0.546
Leptin men (ng/ml)	4.6 (4.9)	82	7.5 (6.9)	78	9.0 (7.4)	92	8.5 (7.3)	79	8.4 (6.8)	81	18.1	4, 50	<0.001	0.592
Leptin women (ng/ml)	12.5 (9.2)	50	16.3 (10.1)	49	20.6 (11.9)	59	20.8 (13.9)	47	18.4 (13.3)	52	11.0	4, 27	<0.001	0.619

* Pillai's Trace statistic *F* value.

Abbreviations: BMI: body mass index, LDLc: low density lipoprotein cholesterol, HDLc: high-density lipoprotein cholesterol, TG: triglycerides, TC: total cholesterol.

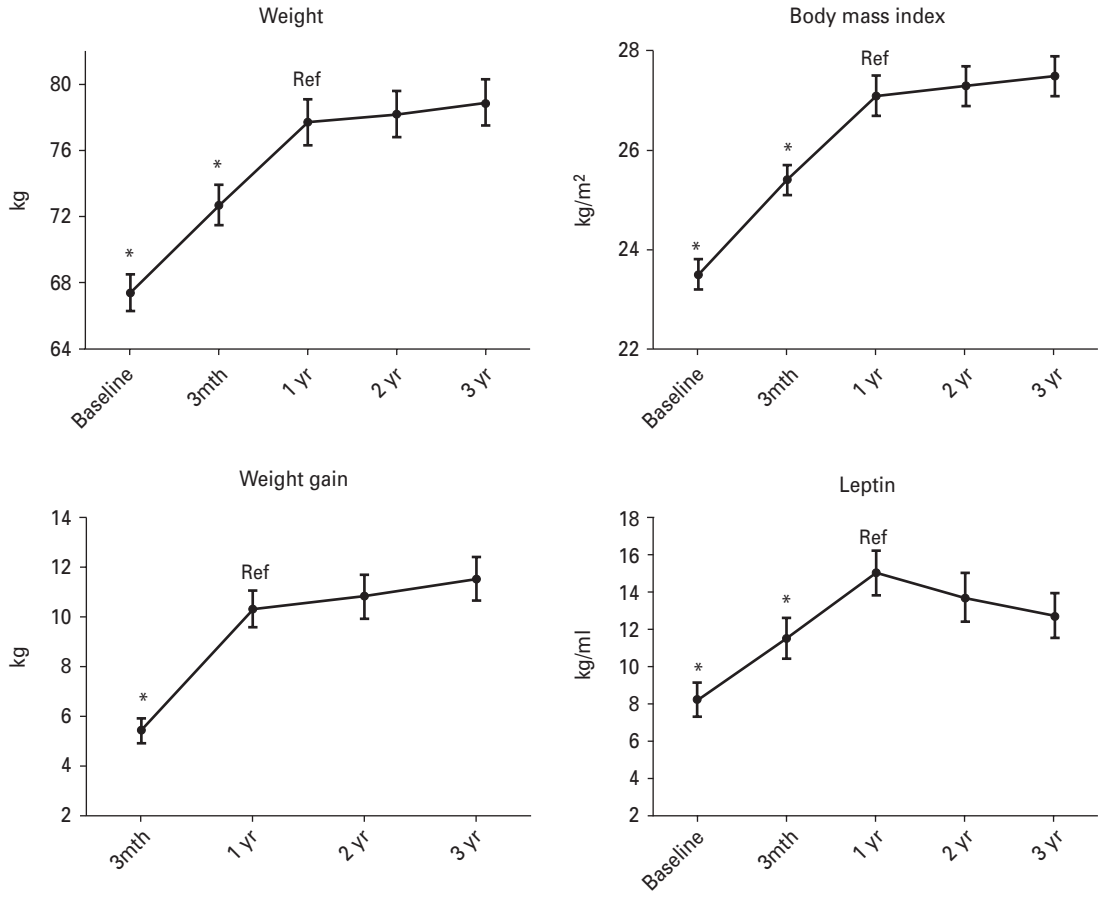

Fig. 1. Mean values of anthropometric measurements and leptin levels at each five points. Error bars represent S.E.M. (standard error of the mean). *=p value <0.05 (one-way ANOVA repeated measures followed by Bonferroni *post hoc* test with the 1 yr value [ref] as the reference time-point).

levels, as an indicator of adipose mass, followed a similar trajectory with a significant increase only during the first 12 mth (see Fig. 1).

In a similar way, the plasma total cholesterol, LDL-cholesterol and triglycerides concentrations increased significantly within the first year and remained relatively constant during the rest of the study period (see Fig. 2). On the contrary, HDL plasma levels remained unchanged during the first months and decreased significantly during the last 2 yr.

The weight increase was significantly correlated with the changes in triglyceride (r=0.34; p<0.001), LDL-C (r=0.22; p=0.024), leptin (r=0.47; p<0.001) and insulin (r=0.36; p<0.001) concentrations. There was a negative correlation between weight gain and the reduction of the HDL-cholesterol levels (r=−0.34; p<0.001). These associations were significant after controlling for sex, age and BMI at baseline.

No significant changes were observed in the mean glucose plasma levels during the first 3 yr of antipsychotic treatment. No statistically significant changes were observed in the mean insulin plasma levels or in the HOMA index, although a trend for an increase was noted during the first 12 mth (see Table 1 and Fig. 3).

Predictors of weight gain

The regression analyses revealed that at short-term (3 mth) a higher risk of weight gain was associated with individuals who initially received olanzapine treatment (β=0.185; t=2.491; p=0.014), male gender (β=0.288; t=3.778; p<0.001) and those patients with a lower BMI (β=−0.285; t=−3.648; p<0.001). These variables accounted for 19% of the variance in weight gain. More detailed information about the predictive regression models is available on request.

After 12 mth these associations were no longer detected and the only clinical variable marginally associated with weight gain was poor social functioning (β=0.159; t=1.957; p=0.052).

At long-term (3 yr), one of the strongest predictors of weight gain was poor social functioning (β=0.246; t=2.441; p<0.016). Those patients with no deficits at 3 yr follow-up gained a mean of 9.4 kg compared to 14.5 kg of those patients with deficits in social function (F=4.758; df=126, 1; p=0.031). The lack of clinical response was also a significant predictor of weight gain. The lack of response for negative symptoms was positively associated with weight gain (β=0.197; t=1.989; p<0.049).

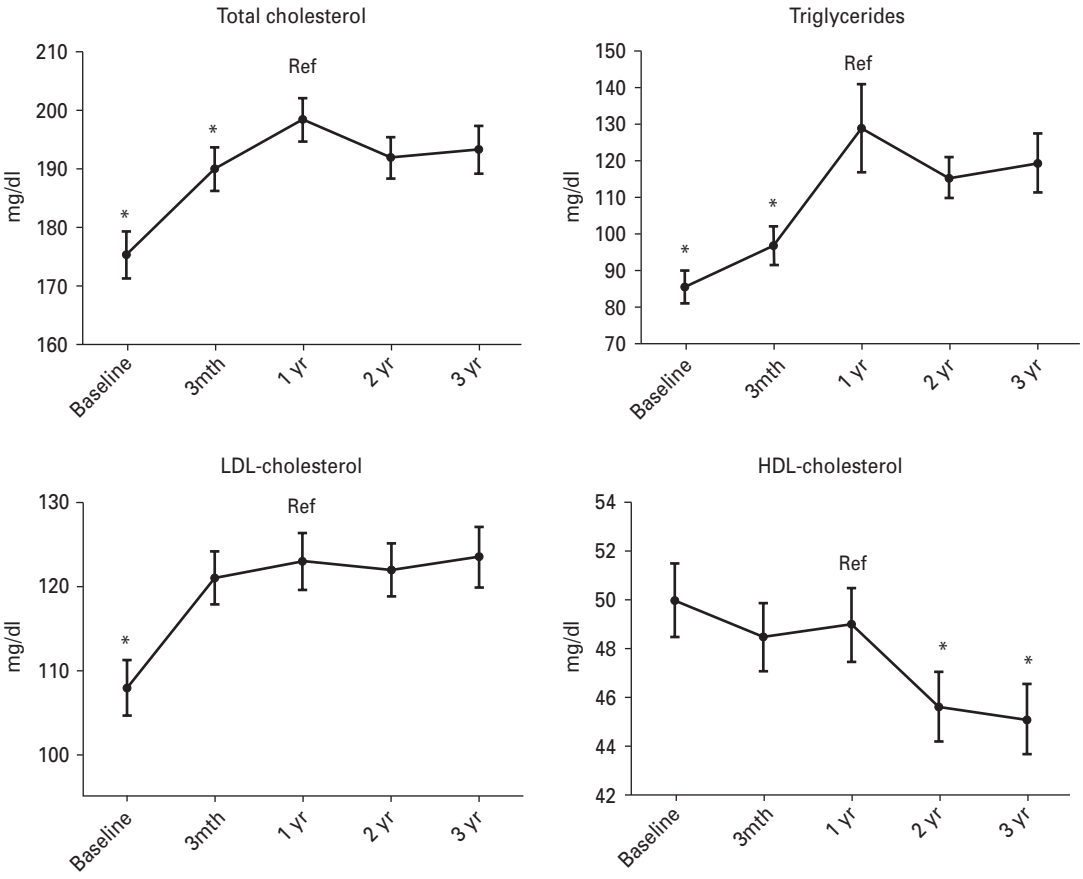

Fig. 2. Mean lipid values at each five points. Error bars represent S.E.M. (standard error of the mean). *=p value <0.05 (one-way ANOVA repeated measures followed by Bonferroni *post hoc* test with the 1 yr value [ref] as the reference time-point).

On the other hand, the subgroup of patients classified as non-responders for positive symptoms gained significantly less weight at the end of the follow-up (β=−0.301; t=−3.525; p<0.001).

Variables that were not associated with weight gain were age, socio-economic status and duration of untreated psychosis.

Incidence of high levels of cholesterol and glucose over 3 yr of antipsychotic treatment

The percentage of patients with clinically elevated triglyceride levels (>150 mg/dl) increased from 4.5 to 22.5% during the 3 yr period (see Table 2). Only one patient had TG levels higher than 500 mg/dl at 1 yr follow-up and he required triglyceride-lowering medications.

The percentage of patients with HDL-cholesterol below 35 also increased significantly from 7.1 to 23% (p<0.001).

No significant changes were observed over the 3 yr interval in the percentage of patients with high total cholesterol or LDL-cholesterol levels (see Table 2).

At baseline one patient had fasting glucose plasma levels above 126 mg/dl, which was not confirmed by subsequent tests. Two individuals developed diabetes type II (fasting glucose plasma level >126 mg/dl) near the end of the study period and were treated with oral anti-diabetic drugs. They had been initially assigned to olanzapine and haloperidol treatment arms and at the time the hyperglycaemia was detected they were taking ziprasidone and amisulpride, respectively. BMI increased from 27.2 to 45.1 kg/m^2 in one case and from 30.5 to 36.5 kg/m^2 in the second. Both had first-degree relatives with type II diabetes.

Other CVD risk factors: tobacco use

The percentage of smokers was very high at baseline (59%) and at the end of the follow-up (64%). The smoking prevalence was higher in men (75%, n=63) than in women (45%; n=24). The mean number of cigarettes smoked a day was similar in males (23 cig/d) and females (22 cig/d).

Discussion

Course of weight gain and metabolic changes

This study allows us to see the 3-yr weight gain trajectory of patients treated with antipsychotic drugs for the first time. The results indicate that the first 12 mth of treatment is a critical period for weight gain and metabolic changes. Interventions that aim to prevent or attenuate these common adverse effects need to start early.

Table 2. Comparison of proportion of subjects with pathologic parameters in weight, glucose and lipid levels at baseline and after the first 3 yr of antipsychotic treatment

	Baseline % (*n*)	3 Yr Follow-up % (*n*)	*N* valid	*p**
Obesity				
BMI>30 kg/m^2	5.2 (7)	31.9 (43)	135	<0.001
Dyslipidaemia				
Cholesterol (mg/dl) >240	6.4 (9)	7.9 (11)	140	0.754
LDL cholesterol (mg/dl) >175	5.3 (6)	5.3 (6)	113	1
HDL cholesterol (mg/dl) <35	7.1 (8)	23 (26)	113	0.001
Triglycerides (mg/dl) >150	4.5 (5)	22.5 (25)	111	<0.001
TC/HDLc ratio >5	8 (9)	29.5 (33)	112	<0.001
Glucose abnormalities				
Glucose >126 mg/dl	0.7 (1)	1.4 (2)	139	1
Glucose >100 mg/dl	5 (7)	9.4 (13)	139	0.238
Tobacco use				
Smokers	58.8 (80)	64 (87)	136	0.210

* McNemar test for repeated measures.
Abbreviations: BMI: body mass index, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TC: total cholesterol.

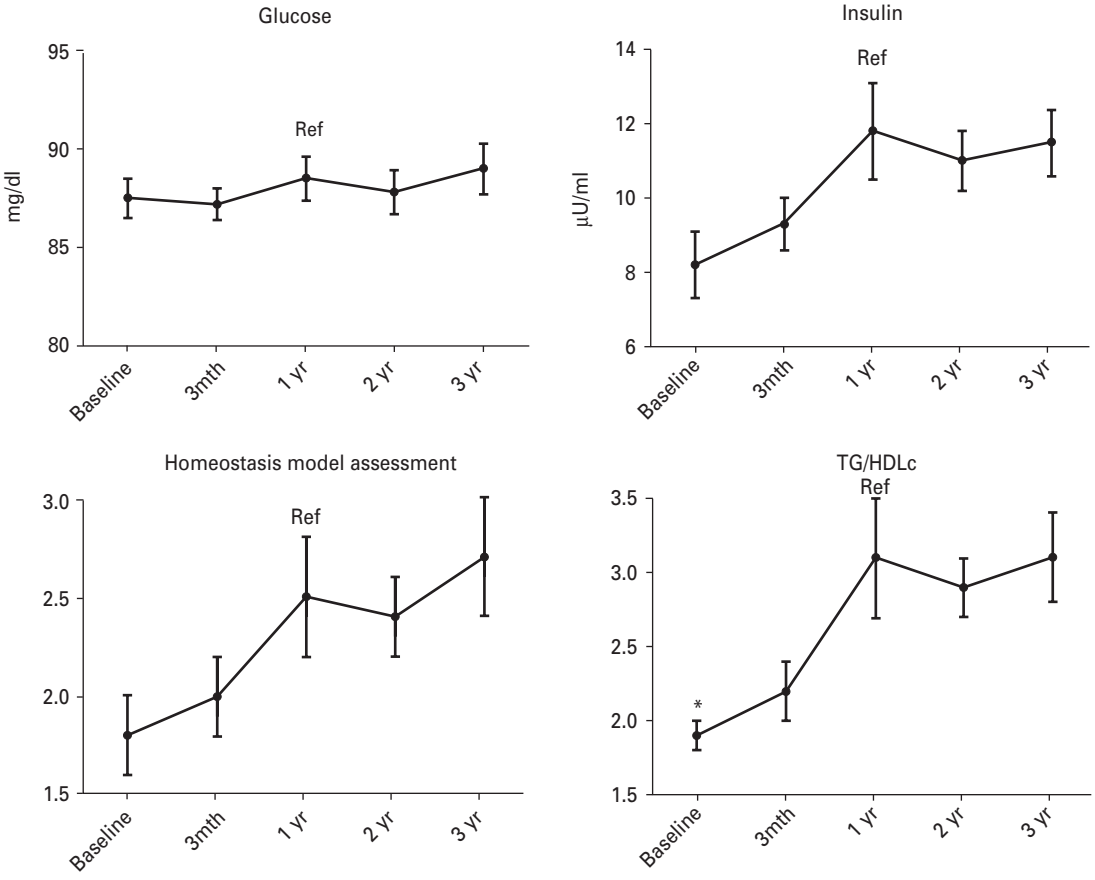

Fig. 3. Mean glycaemic values at each five points. Error bars represent S.E.M. (standard error of the mean). *=p value <0.05 (one-way ANOVA repeated measures followed by Bonferroni *post-hoc* test with the one year value [ref] as the reference time point).

The antipsychotic-induced weight gain course has rarely been investigated beyond the first year (Gentile, 2009). Zipursky et al., (2005) found similar results in a cohort of patients with first-episode psychosis treated with haloperidol and olanzapine. Both treatment groups gained weight rapidly during the first wk of treatment and then the rate of weight gain slowed gradually and stabilized after 1yr. Although the total amount of weight gain is usually lower in chronic populations than in patients with a first episode of psychosis, a similar pattern has been observed. In a large 3-yr prospective study of schizophrenia patients, Novick et al., (2009) reported that most of the weight gain occurred within the first 6 mth of treatment with different atypical antipsychotics. Our results are also consistent with the findings obtained by Kinon et al., (2001) in a retrospective study showing that patients treated with olanzapine reached a plateau after the initial 39 wk. In a 5-yr naturalistic study in patients treated with risperidone Neovius et al. (2007) found that the weight trajectory was steeper initially and then tapered off after 2 yr.

As previously reported in this cohort (Perez-Iglesias et al., 2009), the changes in lipid, insulin and leptin concentrations are significantly correlated with weight gain. The data suggest that interventions targeting weight gain may also prevent lipid and glycaemic abnormalities.

Predictors of weight gain

Predictors of weight gain at short-term were different from those at long-term. The inverse association between pre-treatment BMI and weight gain has been found in most (Kinon et al., 2001; Brecher et al., 2007; Neovius et al., 2007; Strassnig et al., 2007; Saddichha et al., 2008) but not all previous studies (Zipursky et al., 2005; Ahmed et al., 2008). Initially men gained more weight than women, which has been also reported by Ahmed et al., (2008). On the contrary, other studies have found a higher risk of weight gain in females (McEvoy et al., 2007; Neovius et al., 2007) or no sex differences (Zipursky et al., 2005). The finding that patients treated with olanzapine gained more weight during the first wk of treatment has been consistently reported in the literature (Allison et al., 1999; Newcomer, 2005). These short-term predictors might help to identify a sub-group of subjects particularly susceptible to rapid weight gain and who may benefit from early intervention.

At long-term, social functioning was one of the main factors associated with weight gain. The relationship between antipsychotic-induced weight gain and social outcomes has not been as well studied as the other variables. This finding is in agreement with a previous study in patients with personality disorder that reported an association between higher BMI and poor social and functional outcomes (Frankenburg and Zanarini, 2011). It is also consistent with the findings reported by Egger et al., (2007) which showed an improvement in social functioning linked to weight loss in a sample of patients receiving topiramate as a therapy to treat olanzapine-induced weight gain. The adverse impact of poor social functioning on body weight in people suffering from schizophrenia is an important area to explore in the future.

Clinical response was also associated with weight gain at 3 yr follow-up. The lack of response for positive symptoms was negatively correlated with weight gain and the lack of response for negative symptoms was positively correlated with weight gain. From these results we can speculate that those patients with more severe negative symptoms might have a lower level of physical and social activities and therefore they would be at higher risk of weight increase. The finding that those patients with more severe positive symptoms gained significantly less weight maybe in part explained by the lower rate of good adherence by patients in this group (52% of good compliance in non-responding patients *vs.* 75% in patients with good response).

Overall, weight gain was modestly predicted by the main clinical variables in our sample. Changes in body weight are the result of complex interactions between environmental and genetic factors. A possible explanation for the limited prediction of these models may be the lack of inclusion of other variables such us diet, level of physical activity or genetic factors that could influence the amount of weight gain.

Cardiovascular risk factors

It is worth noting that the incidence of type II diabetes in our cohort (5 cases per 1000 person-year) was similar to the incidence of diabetes in young Spanish Caucasian population (8 cases per 1000 person-year) (Valdes et al., 2007; Soriguer et al., 2008). Our findings differ from those reported in most previous studies which have shown a higher risk of diabetes in patients treated with first- or second-generation antipsychotics than in unexposed individuals (Baker et al., 2009; Kessing et al., 2010; Nielsen et al., 2010; Mitchell et al., 2012). Two major factors that could account for this discrepancy are the relatively short exposure time to antipsychotic therapy (3 yr) and the young mean age in our sample (mean age at the end of the follow-up=30.5±7.5). Ethnic differences may also contribute to explain the different findings, as 98% of the sample was white Caucasian, associated with a lower prevalence of diabetes than other population groups.

Nevertheless, only 31% of the patients remained within a normal BMI range at the end of the 3 yr. A high proportion of them were exposed to high levels of triglycerides (22.5%) and low levels of HDL-cholesterol (23%) and two-thirds were smokers. Exposure to these risk factors since early adulthood may have adverse consequences on their long-term cardiovascular health.

A recent publication (Foley and Morley, 2011) has summarized CVD risk factors data from 25 longitudinal studies of patients experiencing their first treated episode of psychosis. The authors concluded that cardiovascular risk increases after first exposure to any antipsychotic drug. However, a definite conclusion about the impact of antipsychotic therapy on cardiovascular risk at long term was not possible to reach given the sparse data beyond 1 yr, the high rates of dropouts in the longer trials and the small sample size of most of these studies.

Strength and limitations

There are several limitations of this study. Firstly, adherence to medication was self-reported and therefore may have been over-estimated. Secondly, a comparison between treatments at long-term was not possible because of the high percentage of treatment switching over the 3 yr period. Frequent changes in antipsychotic treatment are a common pattern in clinical practice and this means that in practice we cannot estimate the effects of single antipsychotics on long-term cardiovascular morbidity. Much larger samples will be needed to estimate the effect of common and complex drug treatment patterns used in clinical practice on long-term cardiovascular outcomes. Thirdly, an important variable, blood pressure, was not measured and a CVD risk score could not be estimated.

However, the strengths of our study are also considerable. The sample studied was a cohort that was followed for 3 yr, one of the longest follow-up studies in first-episode medication-naive patients. The low numbers of dropouts allowed us to accurately estimate the incidence of metabolic adverse events in this population. Finally, the high participation rate implies that the results are generalizable to first-episode psychotic patients in our geographic region.

Conclusion

In summary, the first year of exposure to antipsychotic treatment is a critical period for development of obesity and metabolic abnormalities. Early interventions to moderate the rapid weight gain during the first mth of antipsychotic treatment could potentially help to reduce the cardiovascular disease risks at long-term. Given the high percentage of smokers, tobacco cessation interventions should also be considered a priority for preventing CVD. Moreover, specific interventions targeting this group of people would be advisable as the smoking rate is significantly higher than in the general population of the same age (32.9 *vs.* 64%) and, as opposed to the general population, it is not decreasing.

We are, however, cautious to generalize our findings to other populations as they can be influenced by different variables such as ethnic composition, prevalence of obesity at baseline or adherence to medication. These results need to be confirmed in larger prospective cohorts from different cultural and ethnic groups.

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Conflicts of interest

Prof Crespo-Facorro has received unrestricted research funding from AstraZeneca, Pfizer, Bristol-Myers Squibb and Johnson & Johnson. He has also received honoraria for his participation as a speaker at educational events from Pfizer, Bristol-Myers Squibb and Johnson & Johnson along with consultant fees from Pfizer. Prof Tabarés-Seisdedos has received grants from or acted as a consultant for the following companies: AstraZeneca, Janssen, Eli- Lilly, Lundbeck, Novartis, Pfizer, Sanofi-Aventis and Wyeth. Dr Perez-Iglesias has received support to attend conferences from Lilly.

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