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REVIEW ARTICLE

Weight gain in antipsychotic-naive patients: a review and meta-analysis

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Background. Weight gain is a long-recognized side-effect of antipsychotic (AP) drugs and a major health concern in the treatment of psychosis. The strength of the causal relationship between AP drug exposure and weight gain can only be gauged by a drugs trial conducted on AP-naive patients.

Method. We conducted a review of the literature regarding the amount of weight gain induced by APs in AP-naive patients and carried out a meta-analysis of mean weight gains.

Results. We found 11 primary studies reporting the effects of APs on body weight or body mass index (BMI) in AP-naive patients. The mean body weight and BMI gains in AP-naive patients were highly significant from the first weeks of treatment. When we limited the analysis to studies conducted on patients hospitalized and without any adjunctive treatment potentially affecting weight, the resultant sample showed less heterogeneity and confirmed the final picture of weight gain at around 3.8 kg and 1.2 points BMI.

Conclusions. Weight gain associated with AP therapy in AP-naive patients occurs rapidly in the first few weeks and continues during the following months. Clinicians should be aware of the high probability of causing weight gain in AP-naive patients and should strictly monitor such patients.

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Key words: Antipsychotic agents, antipsychotic-naive, BMI gain, first-episode psychosis, weight gain.

Introduction

Weight gain has long been recognized as a side-effect of antipsychotic (AP) drugs (Allison *et al*. 1999; Lieberman *et al*. 2005). This AP side-effect has recently become a major concern in the treatment of psychosis because weight gain is a potential contributor to increased co-morbidity (Wirshing, 2001), including glucose intolerance, diabetes mellitus (Hedenmalm *et al*. 2002; Scheen & De Hert, 2007), metabolic syndrome (McEvoy *et al*. 2005), sleep apnoea (Wirshing *et al*. 2002) and cardiovascular diseases (Robinson *et al*. 2005). All of these conditions can lead to increased mortality (Kurzthaler & Fleishhacker, 2001; Wirshing, 2001). Furthermore, fear of weight gain is one of the main factors contributing to poor compliance found in AP treatment (Perkins, 1999, 2002), so it may adversely affect the clinical outcome (Allison *et al*. 1999; Allison & Casey, 2001).

The mechanisms by which AP drugs induce weight gain have yet to be fully elucidated. AP antagonism to serotonin or histamine receptors (5-HT2c, H1), which modulate appetite and body weight, has been implicated. Estimates of mean weight gain associated with AP agents have varied greatly and possible confounders could be the extent of previous AP treatment or a history of schizophrenia and other risk factors for weight gain in psychiatric patients (Ganguli *et al*. 2001). There is much interest in determining possible additional risk factors for weight gain associated with AP therapy. Schizophrenia and other psychotic disorders are known to be associated with a higher risk of obesity and metabolic disorders; in particular, the body mass index (BMI) of patients with schizophrenia exceeds the general population estimates (Allison *et al*. 1999; Caballero, 2003; De Hert *et al*. 2006). Patients with schizophrenia or other psychotic disorders have well-recognized lifestyle risk factors for overweight and obesity, such as lack of exercise, sedentary habits and a poor diet (Brown *et al*. 1999; Kelly *et al*. 2005). A study by Ryan *et al*. (2004) observed that, compared with normal controls, higher levels of visceral fat stores were present even in first-episode schizophrenia drug-naive patients.

It emerges from such studies that there is considerable variability among patients in terms of tolerance towards AP side-effects such as weight gain. The amount of weight gain differs considerably from

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patient to patient and the clinically prominent individual differences in drug effects on body weight result from a combination of genetic and environmental influences (Basile *et al*. 2001; American Diabetes Association, 2004). Moreover, the time course of AP weight gain varies greatly between studies considering chronic patients and research on first-episode psychosis (FEP) patients; among the first group weight gain reaches a plateau after the first year of treatment whereas among FEP it seems to go on increasing after the first year of treatment (Alvarez-Jiménez *et al*. 2008; Perez-Iglesias *et al*. 2008*a*). Thus, only studies involving drug-naive patients could provide evidence of a risk of weight gain among patients starting AP therapy; and only drug trials conducted on patients starting AP therapy for the first time are able to detect any causal relationship between AP exposure and weight gain and the time course of weight gain.

We have conducted a review of the literature regarding the amount and time course of weight gain induced by APs in drug-naive patients and carried out a meta-analysis of mean weight gains. To our knowledge, this is the first such meta-analysis on this topic.

Method

Studies were identified by systematic searches from 1997 to July 2008 in Medline, PsycINFO, EMBASE and The Cochrane Library database to identify primary studies describing weight gain in AP-naive patients. Search terms included: antipsychotic agents, drug naive, first episode psychosis, weight gain, and BMI. The titles, abstracts and full text of identified papers were screened for eligibility by two reviewers (B.F.G. and D.G.). The search was supplemented by additional relevant papers identified by a manual search through reference lists from articles retrieved and review articles.

The following criteria were applied for selection: participants in the study were AP-naive at baseline; participants in the study had been treated with APs since baseline; APs were not combined with other medication to reduce the potential weight gain due to AP therapy; participants were aged >15 years; the study presented weight and/or BMI changes during AP treatment as outcome; and the results were published in English as a full report.

Statistical analysis

We analysed the mean weight gain by the standard deviation (S.D.) for all the studies considered. For studies that analysed weight gain in patients treated with various APs, we calculated a mean weight change of the whole sample. For those that did not report any S.D. value, for every analysis we calculated it from the S.D. weighted mean in studies that did. As a control group, for each study we created a sample out of an equal number of subjects. For the control group we considered a mean weight gain of 0.00 kg and the S.D. as the weighted mean of S.D. in the studies considered in each analysis. We performed a first analysis of all studies selected. Then we repeated the analysis considering only studies with a follow-up at $\leqslant 12$ weeks, studies without co-therapy, out-patients and patients with physical co-morbidity within the sample and independent studies to reduce heterogeneity among studies. Finally, we analysed studies grouped by differing follow-up duration, to analyse the time course of weight gain in AP-naive patients.

Data were entered into the Cochrane Collaboration review manager software (RevMan version 4.2) and analysed by RevMan analysis 1.01 (RevMan 2003). Heterogeneity between studies was assessed by the χ^2 test. Individual and pooled weighted mean differences and associated 95% confidence intervals (CIs) were calculated. A fixed-effect model was used in all analyses. We used this model despite the moderate heterogeneity across studies, given that we had no *a priori* reason to hypothesize data coming from different populations and because the main aim of the present analysis was to ascertain the best estimate of a single effect size rather than the range of effect sizes across populations (Munafò & Flint, 2004). We assessed the publication bias visually with funnel plots and statistically with the methods of Egger *et al*. (1997).

Results

The literature search and selection produced 844 studies, 243 of which were retrieved after screening the title and abstracts (Fig. 1). Eighteen of these papers met our criteria. The main reasons for exclusion at this stage were: articles did not report data on body weight gain or did not involve drug-naive patients (199); studies were carried out on a sample with only a percentage of drug-naive patients or they did not report participants' previous drug history (17); studies where olanzapine was combined with the drug to reduce the potential weight gain (fluoxetine, reboxetine, famotidine, betahistine or metformin) (6); case reports (3). One additional paper was identified by checking references to selected papers. In all, 19 papers were included, reporting on 11 studies.

One paper (Wu *et al*. 2007) was excluded because it used the same sample as the previous Wu *et al*. study (2006). Zhang *et al*. (2003) reported data on nearly the same sample as the previous one by Reynolds *et al*. (2002), but the latter paper provided data only on BMI

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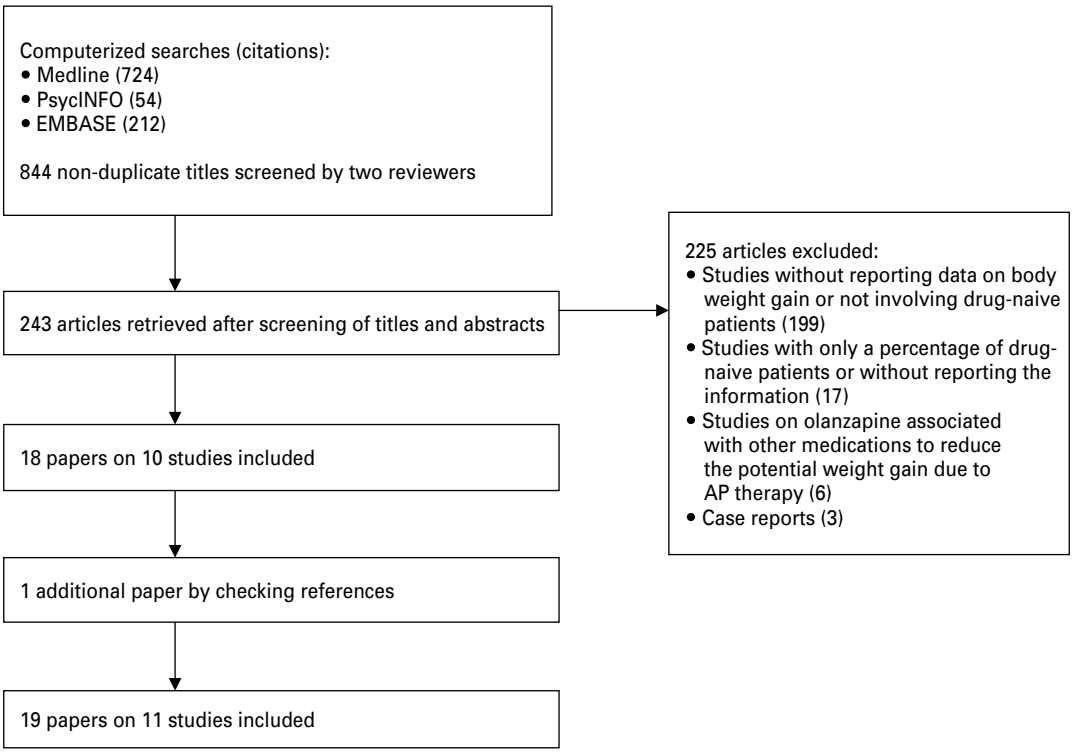

Fig. 1. Selection of studies.

whereas the former also reported data in kg; thus we considered the Reynolds *et al*. paper (2002) for BMI data and the Zhang *et al*. paper (2003) for kg data. Three studies (Saddichha *et al*. 2007*a*, *b*, 2008*b*) were excluded because of preliminary and/or incomplete data in the study by Saddichha *et al*. (2008*a*), two studies (Perez-Iglesias *et al*. 2007, 2008*b*) because of preliminary and/or incomplete data in the study by Perez-Iglesias *et al*. (2008*a*), and one (Reynolds *et al*. 2003) because it referred to a subgroup of patients from the study by Reynolds (2002).

Of the 12 papers selected (Table 1), five reported AP-naive patients' weight gain (in kg) and BMI (Zhang *et al*. 2004; Arranz *et al*. 2007; Perez-Iglesias *et al*. 2008*a*; Saddichha *et al*. 2008*a*; Tarricone *et al*. 2008), four studies reported only BMI values (Reynolds *et al*. 2002; Ryan *et al*. 2004; Templeman *et al*. 2005; Wu *et al*. 2006) and three only the weight gain in kg (Yap *et al*. 2001; Luty *et al*. 2002; Zhang *et al*. 2003).

As shown in Table 1, six studies reported BMI data at 4–8 weeks' follow-up (Reynolds *et al*. 2002; Templeman *et al*. 2005; Wu *et al*. 2006; Arranz *et al*. 2007; Saddichha *et al*. 2008*a*; Tarricone *et al*. 2008) and four studies reported kg data at 4–8 weeks' follow-up (Yap *et al*. 2001; Arranz *et al*. 2007; Saddichha *et al*. 2008*a*; Tarricone *et al*. 2008). Four studies reported BMI data at 10–12 weeks' follow-up (Reynolds *et al*. 2002; Zhang *et al*. 2004; Templeman *et al*. 2005; Perez-Iglesias *et al*. 2008*a*) and three studies reported kg data at 10–12 weeks' follow-up (Zhang *et al*. 2003, 2004; Perez-Iglesias *et al*. 2008*a*). Finally, three studies reported BMI data at 24–48 weeks' follow-up (Ryan *et al*. 2004; Templeman *et al*. 2005; Perez-Iglesias *et al*. 2008*a*), one study reported kg data at 48 weeks' follow-up (Perez-Iglesias *et al*. 2008*a*) and one kg data at 2.5 years' follow-up (Luty *et al*. 2002). Among the studies found, nine reported mean AP doses that are within the optimal therapeutic range as presented in Table 1.

Meta-analysis of BMI main gains

As the first step we calculated the mean BMI gain from analysis of the nine studies selected, in each study considering data from the last observation available. Only two studies lasted more than 12 weeks (Templeman *et al*. 2005; Perez-Iglesias *et al*. 2008*a*). We found a mean BMI increase of 1.97 (95% CI 1.81–2.12, $p < 0.00001$); homogeneity between studies proved to be low (test for heterogeneity: $\chi^2 = 241.26$, df = 8, $p < 0.00001$) (Fig. 2). In the following steps we excluded studies with possible factors affecting heterogeneity. First, we excluded studies that only provided follow-up >12 weeks (Ryan *et al*. 2004). We considered data from the studies by Templeman *et al*. (2005) and Perez-Iglesias *et al*. (2008*a*) at 12 weeks. We found eight studies where analysis resulted in a mean BMI gain of 1.51 (95% CI 1.36–1.67, $p < 0.00001$; test for heterogeneity: $\chi^2 = 42.75$, df = 7, $p < 0.00001$). Then we excluded

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Table 1. *Description of studies on antipsychotic-naive patients*

Study and sponsor	Study population	Design and drugs	Mean weight gain in kg	Mean BMI gain	Other comments
Yap *et al*. (2001) Independent	Twenty-four patients with schizophrenia for ⩽12 months (18) or schizophreniform disorder (six) (DSM-IV) Duration of illness 166.5±111.4 days (range 8–360) Lifetime history of previous AP exposure <3 days Mean age 33.29±9.12 years; 16 (66.7%) males, 19 (79.2%) Chinese, three (12.5%) Malay, two (8.3%) Indian Baseline weight 55.9±12.9 kg	Prospective study, 8 weeks Risperidone (24) Mean dose at day 56: 2.7±1 mg/day (increased from 1 to 2.7±1 mg/day) ($p<0.001$)	Mean increase in body weight from 55.9±12.9 to 57.3±12.4 kg ($p=0.09$)		Nine patients were treated with BDZ and three with antiparkinsonian drugs Exclusion criteria: current and clinically relevant organic, neurological or cardiovascular disease, alcohol or drug abuse within the past 12 months
Luty *et al*. (2002) Independent	Twenty-one patients (14% in-patients and 57% out-patients) with first-episode schizophrenia or schizophreniform disorder (DSM-IV) At follow-up 18 had schizophrenia and three had recovered Mean age 31±9 years; 14 (67%) males, all Scottish Baseline weight 68±10 kg Baseline BMI 23±4	Prospective controlled study, 2.5 years At follow-up, six patients were receiving FGA, 11 SGA and one a mixture; three were on no AP medication. 10 patients had been prescribed AP continuously since baseline	Mean weight gain of 13±10 kg in the 10 patients who had received continuous medication Mean increase in body weight from 68±10 to 78±15 kg ($p=0.0001$) Weight gain greater (but not SS) in patients who had received continuous medication (13±10 kg compared to 7±7 kg)	Mean increase in BMI from 23±4 to 26±5 ($p=0.0002$)[a] Significant increase in body weight in both males and females	In the study period patients had received a mean of 3.1 different APs
Reynolds *et al*. (2002)[b] Independent	One hundred and twenty-three patients with first-episode schizophrenia (DSM-IV) Mean age 26.6±7.7 years; 50 (41%) males, all Chinese Baseline BMI 21.7±2.94	Prospective study, 10 weeks Chlorpromazine (69) Risperidone (46) Clozapine (4) Fluphenazine (3) Sulpiride (1)		Mean increase in BMI of 0.66±0.89 after 6 weeks ($n=123$) and 1.16±1.17 after 10 weeks ($n=117$) Mean increase in BMI in wild-type genotype ($n=96$) of 0.85±0.96 after 6 weeks and 1.38±1.21 after 10 weeks and in the variant genotype ($n=27$) of −0.01±0.60 after 6 weeks and 0.41±1.02 after 10 weeks	No information on concomitant therapies Exclusion criteria: medical or neurological illness and family history of diabetes or eating disorder All received dietetically balanced hospital meals and had the opportunity of 1 h of physical exercise every day

Zhang *et al.* (2003)[b] Independent	One hundred and seventeen in-patients with first-episode schizophrenia (DSM-IV) Duration of illness 1.5 ± 1.2 years Mean age 26 ± 8 years; 58 (50%) males, all Chinese Baseline weight 60 ± 11 kg Baseline BMI 22 ± 3	Prospective study, 10 weeks Chlorpromazine (66) mean dose: 322 ± 74 mg/day Risperidone (43) mean dose: 4 ± 0.5 mg/day Clozapine (4) Fluphenazine (3) Sulpiride (1)	Mean weight gain of 3 ± 3 kg or 6 ± 6% of their baseline body weight	Mean increase in BMI of 1.2 ± 1.2 No significant differences in body weight and change in BMI between chlorpromazine-treated group (1.3 ± 1 kg/m²) and risperidone-treated group (1.2 ± 1.5 kg/m²) or between male (1.1 ± 1.3 kg/m²) and female (1.2 ± 1.2 kg/m²) patients Baseline BMI was significantly associated with weight gain ($p = 0.0001$), age was inversely correlated with weight gain ($p = 0.03$) in normal-weight group (BMI 17–23). No other clinical variables including drug dosage were associated with weight gain	No information on concomitant therapies The patients had no other mental or neurological disease, no eating disorder, obesity, diabetes, hypertension, drug or alcohol abuse All patients received dietetically balanced hospital meals
Ryan *et al.* (2004) Pfizer	Nineteen hospitalized patients with first-episode schizophrenia (DSM-IV) Mean age 31 ± 2.5 years; 15 (79%) males, all Caucasian Baseline BMI 24.6 ± 0.73	Prospective controlled study, 24 weeks Risperidone (12) mean dose: 3.5 ± 0.3 mg/day Olanzapine (7) mean dose: 11.2 ± 1.7 mg/day Control group (19)		Mean increase in BMI in treated patients from 24.6 ± 0.73 ($n = 19$) to 29.4 ± 0.82 ($n = 16$) ($p < 0.04$) Significant difference of BMI between the three groups (control, pretreatment, post-treatment) Treatment resulted in a significant increase in BMI and there are no differences between controls and patients in term of pretreatment levels of BMI. BMI increased equally with the two drugs	No information on concomitant therapies None had co-morbid DSM-IV diagnoses and all were physically healthy
Zhang *et al.* (2004) Pfizer	Forty-six in-patients with first-episode schizophrenia (DSM-IV) Mean age 26.5 ± 6.6 years; 27 (59%) males, all Chinese Baseline weight 56.7 ± 11.4 kg Baseline BMI 20.5 ± 3.5	Prospective controlled study, 10 weeks Risperidone (30), mean dose: 4.8 ± 0.9 mg/day Chlorpromazine (15) mean dose: 480 ± 122.2 mg/day Quetiapine (1) dose 600 mg Control healthy group (38)	Significantly more weight gain in the treated group compared to the control group (4.64 ± 3.39 kg), $p < 0.05$	Significantly more weight gain in the treated group compared to the control group (1.69 ± 1.2), $p < 0.01$. From 20.5 ± 3.5 to 22.2 ± 3.4 For BMI no significant interaction with gender. No significant correlation between the changes in body fat and clinical features including age and AP dose	Diazepam or anticholinergic drugs for EPS allowed They had no other mental or neurological disease, eating disorder, diabetes mellitus, hypertension or history of alcohol or substance misuse All received dietetically balanced hospital meals

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Table 1 (*cont.*)

Study and sponsor	Study population	Design and drugs	Mean weight gain in kg	Mean BMI gain	Other comments
Templeman *et al.* (2005) Independent	Seventy-three patients with first psychotic episode Mean age 25.2 ± 0.78 years; 55 (75%) males, all Caucasian Baseline BMI 21.9 ± 0.43	Prospective study, 32 weeks Risperidone (26) Olanzapine (19) Haloperidol (10) Quetiapine (11) Ziprasidone (6) Amisulpride (1)		Mean increase in BMI of 1.67 ± 0.13 at 6 weeks (n = 71), 2.28 ± 0.19 at 12 weeks (n = 67) and 4.04 ± 0.42 at 32 weeks (n = 58) Age, but not initial BMI, significant confounding effect on change in BMI at 6 weeks and 3 months	None of the patients had received concomitant therapies with APs, ADs or mood stabilizers Drug treatment was reviewed after 6 weeks and changed as required Excluded if co-morbid DSM-IV diagnosis or substance abuse or dependence or with any physical illness (blood test within normal limits)
Wu *et al.* (2006) Independent	One hundred and twelve in-patients with first-episode schizophrenia (DSM-IV) Duration of illness (months): clozapine 3.2 ± 1.1, olanzapine 1.9 ± 0.7, risperidone 2.6 ± 0.7, sulpiride 2.4 ± 0.8 Mean age 34.9 ± 10.2 years; 56 (50%) males, all Chinese Baseline BMI 20.75 ± 0.4	Prospective randomized controlled study, 8 weeks Clozapine (30) dose: 200–400 mg/day Olanzapine (24) dose: 10–20 mg/day Risperidone (29) dose: 2–5 mg/day Sulpiride (29) dose: 600–1000 mg/day		Mean increase in BMI from 21.14 ± 0.48 to 22.89 ± 0.41 with clozapine (p = 0.008); from 20.65 ± 0.33 to 21.56 ± 0.33 with olanzapine (p = 0.009); from 20.64 ± 0.44 to 20.83 ± 0.45 with risperidone (p = 0.07); and from 20.55 ± 0.33 to 21.21 ± 0.34 with sulpiride (p = 0.026) Elevated BMI found in 20% of patients (n = 6) with clozapine; 17% (n = 4) with olanzapine	Triexifenidile and lorazepam were allowed No recreational drugs before enrolment, excluded if pregnant or lactating, mental retardation, additive disorder, systemic diseases or other medical conditions such as diabetes mellitus, dyslipidaemia, cardiovascular diseases, and hypertension. Baseline normal fasting glucose, insulin, C-peptide, cholesterol, triglycerides; nine patients had family history of type II diabetes All had the same diet but not involved in weight reduction diets or programmes

Arranz *et al.* (2007) Eli Lilly	Thirty-eight in-patients with first-episode paranoid schizophrenia (17), schizophreniform disorder (8), schizo-affective disorder (4), acute psychosis (4), psychotic disorder NOS (3) and bipolar disorder (2) (DSM-IV-TR) Mean age 24.4 ± 7 years; 27 (71%) male, all Spanish Baseline weight 64.4 ± 10.6 kg Baseline BMI 21.75 ± 2.97	Randomized open-label study, 6 weeks Olanzapine tablets (19) mean dose: 13.8 ± 6 mg/day Olanzapine orally disintegrating formulation (19) mean dose: 15.8 ± 8 mg/day	Mean weight gain of 4.8 ± 2.63 kg Significant higher mean weight gain in tablets group (6.3 ± 1.9 kg) compared to orally disintegrating formulation (3.3 ± 3.2 kg), $p = 0.009$	Mean increase in BMI of 1.6 Significant higher mean increase in BMI in tablets group (2.1; from 22.3 ± 3.3 to 24.4 ± 3.3) compared to orally disintegrating formulation (1.1; from 21.2 ± 2.6 to 22.3 ± 2.5), $p = 0.036$ At baseline, six patients had BMI < 18.5; they were equally distributed between both olanzapine groups (three patients in each group), thus avoiding the possible bias of the reported weight gain being attributed to the effect of low BMI in one of our olanzapine groups Age and sex did not show any significant influence in either weight or BMI increase	No concomitant medications allowed Dietary and exercise constant
Perez-Iglesias *et al.* (2008*a*) Independent	One hundred and sixty-four patients with first-episode schizophrenia (103), schizophreniform disorder (38), psychosis NOS (11), brief psychosis (7) (DSM-IV) Duration of untreated psychosis (months): haloperidol 15.3 ± 30.9, olanzapine 12.1 ± 29.4, risperidone 13.9 ± 22.6 Mean age 27 years (15.4–48.3); 103 (62%) males, 96% Caucasian Baseline weight 67 ± 12.8 kg Baseline BMI 23.1 ± 3.5	Prospective, randomized, clinical study, 48 weeks Haloperidol (52) mean dose at 12 weeks 4.7 ± 2, at 1 year 2.9 ± 1.4 mg/day Olanzapine (54) mean dose at 12 weeks 13.3 ± 4.7, at 1 year 10.1 ± 3.9 mg/day Risperidone (58) mean dose at 12 weeks 4 ± 1.6, at 1 year 3.6 ± 1.9 mg/day	Mean weight gain of 5.8 ± 5.4 kg after 12 weeks and 10.5 ± 8.2 kg after 48 weeks Mean weight gain of 4.18 ± 5.49 at 12 weeks and 10.65 ± 7.66 at 1 year with haloperidol; of 7.19 ± 5.26 at 12 weeks and 11.22 ± 7.99 at 1 year with olanzapine; of 6.03 ± 5 at 12 weeks and 9.46 ± 8.99 at 1 year with risperidone At baseline 27.1% had excess weight (4.5% obese), at 12 weeks 47.6% (9% obese) and at 1 year 60.4% (25.7% obese)	Mean increase in BMI of 1.99 ± 17.4 after 12 weeks and of 3.56 ± 2.89 after 48 weeks Mean increase in BMI of 1.43 ± 1.84 at 12 weeks and 3.74 ± 2.6 at 1 year with haloperidol; of 2.51 ± 1.78 at 12 weeks and 3.97 ± 2.79 at 1 year with olanzapine; of 2 ± 1.6 at 12 weeks and 3.25 ± 3.07 at 1 year with risperidone	AD (sertraline) used in 14 patients, lithium in two patients; BDZ, hypnotics and anticholinergics were permitted if clinically needed Excluded if drug dependence, mental retardation, having a serious medical illness, were in good general health and none were receiving drugs that potentially could influence their weight Advice on diet, exercise and lifestyle was given to all patients Forty-nine needed treatment switch

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Table 1 (*cont.*)

Study and sponsor	Study population	Design and drugs	Mean weight gain in kg	Mean BMI gain	Other comments
Saddichha *et al.* (2008*a*) Independent	Ninety-nine in-patients with first-episode schizophrenia: paranoid schizophrenia (66), undifferentiated schizophrenia (33) (DSM-IV) Duration of untreated illness 20.5 ± 18.5 months Mean age 26.1 ± 5.6 years; 52 (52%) males, all Indian Baseline weight 48.5 ± 9.5 kg Baseline BMI 19.4 ± 3	Prospective, randomized, controlled, double-blind study, 6 weeks Olanzapine (35) mean dose: 16.5 ± 4.6 mg/day Risperidone (33) mean dose: 4.4 ± 1.2 mg/day Haloperidol (31) mean dose: 13.4 ± 3.6 mg/day Control healthy group (51)	Mean weight gain of 3.9 ± 2.7 kg AP use ($p < 0.001$) associated with greater increase in weight and BMI Olanzapine had greater clinically significant (>7%) weight gain compared to risperidone and haloperidol Among APs, most of the olanzapine-treated patients showed significant weight gain (77.1%) compared with both risperidone (63.6%) and haloperidol (22.6%)	Mean increase in BMI of 1.6 ± 1.2 Waist circumference ($p < 0.01$), weight ($p < 0.01$) at baseline, the disease process ($p < 0.001$) and AP use ($p < 0.001$) were associated with greater increase in weight and BMI Lower BMI at baseline and diagnosis of undifferentiated schizophrenia were associated with AP-induced weight gain	No drugs that could influence weight were allowed All patients received the same diet and daily regimen Excluded if other psychiatric co-morbidity history of severe physical illness, alcohol and substance abuse or dependence, history of pre-existing diabetes or hypertension or family history of hypertension or diabetes
Tarricone *et al.* (2008) Independent	Fifteen out-patients with schizophrenia (10) or mood disorder (5) (DSM-IV) Mean age 43.9 years (18–80); eight (53%) males, all Caucasian Baseline weight 69.4 ± 15 kg Baseline BMI 24.9 ± 4.4	Prospective study, 4 weeks Olanzapine (7) mean dose: 10 ± 9 mg/day Risperidone (7) mean dose: 2 ± 2 mg/day Quetiapine (1) dose: 200 mg/day	Mean increase in body weight from 69.4 ± 15 to 71.9 ± 15.1 kg ($p = 0.02$)	Mean increase in BMI from 24.9 ± 4.4 to 25.8 ± 4.6 ($p = 0.017$) Baseline BMI did not affect weight, waist circumference, blood pressure, lipid and glucose changes	ADs were allowed Baseline mean metabolic parameters within normal range

BMI, Body mass index; NOS, not otherwise specified; AP, antipsychotic; FGA, first-generation AP; SGA, second-generation AP; SS, statistically significant difference; AD, antidepressant; BDZ, benzodiazepine; EPS, extrapyramidal symptoms.

[a] BMI data from the Luty *et al.* study (2002) were not considered because they are given for the whole sample, including patients who discontinued AP treatment during the follow-up.

[b] These two studies had almost the same sample; we used for the BMI data of Reynolds *et al.* (2002) and the kg data of Zhang *et al.* (2003).

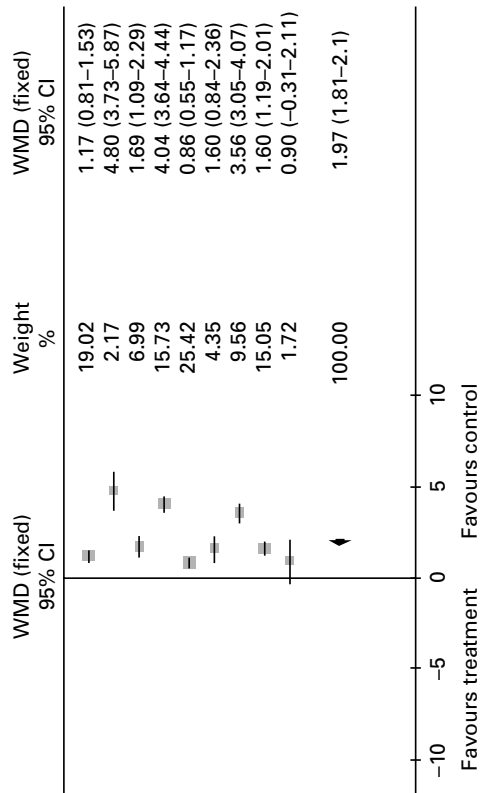

Fig. 2. Mean body mass index gain in antipsychotic-naive patients.

studies with co-therapies having a potential side-effect on body weight (see Table 1) (Perez-Iglesias *et al*. 2008*a*; Tarricone *et al*. 2008); and we found six studies where analysis resulted in a mean BMI gain of 1.43 (95% CI 1.32–1.53, $p<0.00001$; test for heterogeneity: $\chi^2=108.65$, df = 5, $p<0.00001$). At this point, we excluded studies carried out on non-hospitalized patients (Templeman *et al*. 2005) to reduce the possible effect of unbalanced meals on body weight, and we found five studies on hospitalized patients, resulting in a mean BMI gain of 1.18 (95% CI 1.05–1.30, $p<0.00001$; test for heterogeneity: $\chi^2=26.83$, df = 4, $p<0.0001$). Among the five studies on hospitalized patients we then excluded the study by Arranz *et al*. (2007), which did not specify whether patients with physical co-morbidity were excluded, and we found a mean BMI gain of 1.14 (95% CI 1.01–1.27, $p<0.00001$; test for heterogeneity: $\chi^2=23.13$, df = 3, $p<0.0001$). Finally, we excluded three sponsored studies (Reynolds *et al*. 2002; Wu *et al*. 2006; Saddichha *et al*. 2008*a*), resulting in a mean BMI gain of 1.08 (95% CI 0.95–1.22, $p<0.00001$; test for heterogeneity: $\chi^2=17.30$, df = 2, $p=0.0002$).

We also analysed the mean BMI time course considering study data at different times of follow-up. Three studies that reported data at different times of follow-up were considered for all such follow-up evaluations (Reynolds *et al*. 2002; Templeman *et al*. 2005; Perez-Iglesias *et al*. 2008*a*). In view of the low number of studies in the sample, we decided to analyse the mean weighted BMI gains from studies at three different times of follow-up (Fig. 3) and found a continuous rise in the weighted mean BMI; for studies lasting 4–8 weeks (Reynolds *et al*. 2002; Templeman *et al*. 2005; Wu *et al*. 2006; Arranz *et al*. 2007; Saddichha *et al*. 2008*a*; Tarricone *et al*. 2008) we found a mean BMI gain of 1.15 (95% CI 1.06–1.24, $p<0.00001$; test for heterogeneity: $\chi^2=86.14$, df = 5, $p<0.00001$); for studies lasting 10–12 weeks (Reynolds *et al*. 2002; Zhang *et al*. 2004; Templeman *et al*. 2005; Perez-Iglesias *et al*. 2008*a*) we found a mean BMI gain of 1.80 (95% CI 1.62–1.97, $p<0.00001$; test for heterogeneity: $\chi^2=26.01$, df = 3, $p<0.00001$); and for studies lasting 24–48 weeks (Ryan *et al*. 2004; Templeman *et al*. 2005; Perez-Iglesias *et al*. 2008*a*) we found a mean BMI gain of 3.87 (95% CI 3.48–4.26, $p<0.00001$), and here homogeneity between studies proved to be high (test for heterogeneity: $\chi^2=2.88$, df = 2, $p=0.24$).

Meta-analysis of weight gain in kg

Overall, from analysis of the eight studies selected, considering data at the last observation available for every study, the mean weight gain was 4.85 kg (95% CI 4.23–5.47, $p<0.00001$); homogeneity among

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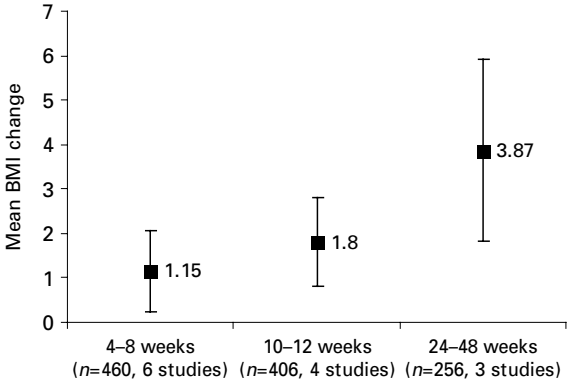

Fig. 3. Body mass index (BMI) mean change at three different follow-up times.

the studies proved to be low (test for heterogeneity: $\chi^2 = 76.91$, df = 7, $p < 0.00001$). We analysed studies reporting weight gain in kg following the same steps reported above for BMI studies and found that the heterogeneity decreased, consistently with the BMI analyses, and that weight gain in kg was directly correlated with the duration of AP treatment (data available on request).

Publication bias

The funnel plot (not shown, available on request) carried out on all BMI studies included in Fig. 1 did not suggest any evidence of publication bias. This finding is confirmed by Egger's regression test analysis ($\beta = 0.31$, $p = 0.411$). The funnel plot on the kg studies included in Fig. 3 was asymmetric but the Egger analysis did not find any publication bias ($\beta = -0.41$, $p = 0.32$).

Discussion

Our findings clearly show a rapid, highly significant and continuously growing weight gain in patients treated for the first time with AP drugs. To our knowledge, this is the first systematic review and meta-analysis of weight gain in AP-naive patients.

We found that weight gain due to AP therapy in AP-naive patients is highly significant from the first months of treatment. The exclusion of studies with adjunctive risk factors, such as co-therapies with a body-weight effect or out-patient status possibly leading to an unbalanced diet, consolidates the causal role of AP drugs on our weight gain findings at around 3.8 kg and 1.2 points BMI within the first 12 weeks of treatment.

Moreover, in analysing the time course of kg and BMI mean increases we found that AP-naive patients' body weight gain increases continuously during AP treatment. We found that heterogeneity among studies with a longer follow-up was low, although the mean kg and BMI gains were still highly significant.

Our results show that even in AP-naive patients weight gain is prominent from the first weeks of treatment, as Allison *et al*. (1999) found in long-term AP-treated patients, where weight gain occurred after a mean of 10 weeks of treatment. Moreover, our results add evidence for the causal role of AP in weight gain, as the previous meta-analysis on this topic (Allison *et al*. 1999) was carried out on long-term AP-treated patients, without considering the role of possible adjunctive risk factors and not reporting the BMI change but only the weight gain in kg. Some studies have noted that FEP patients treated with APs have a higher risk of gaining weight than patients suffering from chronic psychosis (Wetterling & Mussigbrodt, 1999; Kelly *et al*. 2005; Alvarez-Jiménez *et al*. 2008). As a result, it has been posited that patients previously unexposed to AP medication are particularly vulnerable to this AP side-effect (Wetterling & Mussigbrodt, 1999; Basson *et al*. 2001; Kinon *et al*. 2001; Meyer, 2002). The results of our meta-analysis, rigorously including all AP-naive samples, now provide conclusive evidence that weight gain associated with AP therapy in AP-naive patients is prominent and occurs rapidly within the first few weeks. Thus, clinicians should be aware of the high probability of causing weight gain in AP-naive patients and should strictly monitor such patients and also give them dietary counselling at the earliest opportunity.

Our findings also show that weight gain is a continuous process in drug-naive patients. This result is consistent with findings from the few studies that carried out more than one observation at the follow-up (Reynolds *et al*. 2002; Templeman *et al*. 2005; Perez-Iglesias *et al*. 2008*a*). Our meta-analysis does not prove that weight gain reaches a plateau, as suggested for chronic long-treated patients (Henderson *et al*. 2000). The Perez-Iglesias *et al*. (2008*a*) randomized control trial on AP-naive patients extending over 1 year of continuous AP treatment showed that weight gain was faster during the first 12 weeks of treatment and then plateaued. However, there are too few studies on AP-naive patients lasting more than 12 weeks to confirm the possibility that weight gain reaches a plateau when a patient is receiving long-term treatment, and the timing of any such plateau is still controversial and requires further investigation (Wirshing *et al*. 1999; Taylor & McAskill, 2000; McGavin & Goa, 2002; McIntyre *et al*. 2003; Lee *et al*. 2004; Wirshing, 2004; Gentile, 2006; Brecher *et al*. 2007; Henderson, 2007).

The seminal Allison *et al*. (1999) review reported that, in long-term AP-treated patients, weight gain was highly variable among different APs; in their review the drugs most associated with this side-effect

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were clozapine and olanzapine (4–4.5 kg over 10 weeks). Unfortunately, the studies that have examined weight gain in AP-naive patients receiving AP drugs are still too few to distinguish clearly differences in weight gain-inducing potential among the different APs. Moreover, risperidone and olanzapine are the AP drugs most analysed in these studies, whereas the results on other APs are insufficient to draw any definitive conclusions. Although we were unable to perform a direct comparison among the different APs, the studies reviewed indicated that weight gain occurs with all medication.

Limitations

This is the first meta-analysis of weight gain in AP-naive patients. Although AP treatment should be initiated as soon as psychotic symptoms are recognized (Kane *et al*. 2003; Kelly *et al*. 2005), therapy for first-episode schizophrenia has been poorly studied by controlled clinical trials and many studies focus on the efficacy rather than the safety of APs. The large majority of data on weight gain are generated from short-term studies on long-term treated patients and this situation potentially represents a significant bias in identifying the true effects of APs on patients' body weight. In addition, a large proportion of patients treated with APs receive multiple psychotropic medications for concomitant symptoms, and these medications (e.g. mood stabilizers and antidepressants) are frequently associated with weight gain (Kinon *et al*. 2001; Meyer, 2002). Our meta-analysis reports data on weight gain due to AP treatment in a sample of truly AP-naive in-patients, without adjunctive drug therapy. However, our review has several limitations. First, because of the small number of studies found, we could only check a few possible risk factors for weight gain. Several clinical characteristics of the patients included in these studies were not reported and this limited the possibility of looking further at the effect of weight gain in AP-naive patients. For example, most studies did not report the percentage of patients who were underweight, but only said that patients were on average in the normal BMI range at baseline, and did not report data about previous therapies with drugs that can potentially influence body weight. Again, we calculated standard deviations for studies that did not report them, taking a weighted mean of the standard deviation from the studies that did. We created a control group using the mean of the number of patients from all studies considered. For the control group we considered a mean weight gain of 0.00 kg and 0.0 BMI, similar to the weight gain that was found in the meta-analysis by Allison *et al*. (1999) after placebo (−0.5 kg); the S.D. was considered as the weighted mean S.D. of the studies considered in that analysis. This method may have inflated the results but only in the direction of significance, not in the direction of effect size. Moreover, we retrieved studies published in the past 11 years to avoid duplicating the results of Allison *et al*.'s meta-analysis (1999); this may have led us to miss some studies. Finally, our results on weight gain in kg need to be interpreted with caution because there was evidence of funnel plot asymmetry; however, the Egger analysis did not seem to find any publication bias.

Conclusions

Overall, the studies reviewed clearly show a causal relationship between AP treatment and weight gain because: (1) the studies were carried out on AP-naive patients; (2) the weight gain set in during the first 12 weeks of treatment; and (3) the weight gain was notable even when patients with co-therapy and with unbalanced meals were excluded. Our finding that weight gain sets in early and increases continually in AP-naive patients during AP treatment should encourage clinicians to set up an early weight-monitoring programme and to continue this as long as AP treatment lasts.

Weight gain is a significant long-term health issue because it is associated with insulin resistance and the resultant metabolic effects such as elevated triglycerides, diabetes and hypertension, all of which may increase the risk of cardiovascular disease (Haupt, 2006) and trigger well-established long-term medical consequences. Overweight is also a problem of great concern, particularly in young people, because of the substantial negative impact it has on patients' quality of life, giving rise to poor self-esteem and lack of acceptance in public places, and such distress can lead to low adherence to treatment (Haupt, 2006). Furthermore, unlike extrapyramidal motor side-effects, weight gain and other metabolic side-effects have no well-established treatments (Robinson *et al*. 2005). Thus it seems that young people at their first episode of psychosis are at high risk of morbidity and mortality with AP therapy (Addington *et al*. 2003). Innovative approaches are called for, aimed at achieving long-term compensatory weight loss (Addington *et al*. 2003). As indicated by Alvarez-Jimenez *et al*. (2006), early behavioural intervention (diet, education, and exercise) seems to be effective in weight control and needs to be initiated before ascertainment of weight gain.

Declaration of Interest

None.

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