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# Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis

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**Abstract**

Weight gain is a clinically important side effect of antipsychotic drug therapy. The aim of this study was to determine the effect of the antidiabetic drug metformin on antipsychotic-induced weight gain in non-diabetic patients. In a systematic literature review we identified 195 citations from which seven randomized, placebo-controlled studies (398 patients) were included in the final analysis. Studies in adults ($n = 5$) and in children ($n = 2$) were analysed separately. Compared with placebo, metformin treatment caused a significant body weight reduction in adult non-diabetic patients treated with atypical antipsychotics (4.8%, 95% CI 1.6 to 8.0) and in children (4.1%, 95% CI 2.2 to 6.0). There was evidence of substantial heterogeneity among studies, and when the analysis was restricted to patients with a manifest (>10%) body weight increase prior to randomisation metformin reduced weight by 7.5% (95% CI 2.9 to 12.0). The effect was larger in Asians (7.8%, 95% CI 4.4 to 11.2) than in Hispanics (2.0%, 95% CI 0.7 to 3.3). In conclusion, metformin has a pronounced weight-reducing effect in antipsychotic-treated patients, especially in those with a manifest weight gain. Although direct comparisons are lacking, the observed effect on body weight compares favourably with the effect of sibutramine and orlistat, approved for weight reduction. However, metformin is not approved for use in non-diabetic patients and it is still not generally advisable to recommend metformin to counteract antipsychotic-induced weight gain.

**Keywords**

antipsychotic agents, body weight, metformin, meta-analysis

## Introduction

Weight gain is a common and clinically relevant side effect of some typical and atypical antipsychotic drugs (Baptista et al., 2002). The use of atypical antipsychotic agents is also associated with increased insulin resistance, hyperglycaemia and metabolic dysfunction (Baptista et al., 2002). In addition to the increased risk of type 2 diabetes and development of cardiovascular disease, excessive weight gain may lead to impaired compliance.

In recent years, metformin treatment has been suggested to prevent or reverse weight gain induced by antipsychotic agents, despite no symptoms or signs of diabetes mellitus (Baptista, 1999). Metformin is an antidiabetic agent used in type 2 diabetes, preferably in obese patients. It inhibits the hepatic synthesis of glucose and decreases peripheral insulin resistance (Dunn and Peters, 1995; Hundal and Inzucchi, 2003). In obese diabetic patients metformin treatment has been associated with some weight reduction, but the mechanism is unknown (Hundal and Inzucchi, 2003). Other antidiabetics, such as rosiglitazone, have also been tested for the prevention of weight gain and metabolic control in patients on antipsychotic agents, but have not been effective in the same way as metformin (Baptista et al., 2009).

Lactic acidosis is a rare but severe adverse reaction to metformin, associated with a high mortality (Dunn and Peters, 1995). Metformin is only approved for use in patients with diabetes, and use in non-diabetic patients is presently considered an 'off-label' prescription. However, metformin has previously been used in non-diabetic patients, for example, to induce ovulation in women with polycystic ovary syndrome (Ng et al., 2001) and for the prevention of type 2 diabetes in predisposed patients (Lilly and Godwin, 2009).

The aim of this study was to determine the effect of metformin treatment on antipsychotic-induced weight gain in non-diabetic patients, by means of a systematic review and a meta-analysis.

## Methods

### *Search strategy*

The literature search was conducted in PubMed and EMBASE (finished 20 July 2009). Searches were not restricted to time or language. Text words and keywords included in the search strategy are presented in the Appendix. Briefly, the word 'metformin' was combined with different antipsychotic agents.

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### Study selection criteria

One reviewer (LBB) initially evaluated the abstracts from the literature search. Included studies had to meet the following criteria: (1) clinical, double-blind randomized controlled trial; (2) two groups of non-diabetic patients where one group was treated with metformin and the other with placebo; (3) all patients had to be on antipsychotic drug therapy; (4) the placebo group and the metformin group that were compared should have the same kind of treatment and care in all other ways (for example, education regarding diet and lifestyle changes).

In case of any ambiguity, authors were contacted for additional information.

### Data extraction

Data from included studies were extracted and summarized independently by two reviewers (JDL and LBB). Recorded data included characteristics of the studies, demographic data, and weight changes in patients allocated to metformin or placebo. Any discrepancies were resolved by consensus.

### Statistical methods

The primary outcome measure used in the meta-analysis was weight change between baseline and last available follow-up, expressed as percentage of baseline body weight. If percentage weight change was not presented, it was calculated by dividing the absolute weight change and associated standard deviation (SD) by the mean baseline weight in each treatment group. When necessary, SDs were calculated from confidence intervals (CI) and sample sizes. The studies were weighted using the inverse variance method and the effect of metformin on body weight was expressed as mean difference (MD) between the metformin and placebo groups. Analysis results associated with $p$ values $<0.05$ (two-sided test) were considered statistically significant. Owing to the possible non-compatibility of results derived from adults and children, studies in adults and paediatric patient populations were analysed separately.

Homogeneity among studies was tested by means of Cochran's $Q$ test and calculation of the variation across studies attributable to heterogeneity rather than chance ($I^2$). When substantial heterogeneity was demonstrated (defined as a Cochran $Q$ test $p$ value $<0.1$ or a $I^2$ value $>25\%$) or when fewer than five studies were included in the analysis, a random-effects model was used to calculate the overall mean difference; otherwise a fixed-effect model was used.

Sensitivity analyses were performed to assess the influence of various study characteristics on the observed metformin effect. Owing to the small number of paediatric studies identified, these analyses were restricted to studies in adults. For the sensitivity analyses, the studies were stratified according to timing of metformin treatment relative to antipsychotic therapy (patients already on atypical antipsychotics or both therapies commenced simultaneously) and ethnicity (Asian or Hispanic) and the meta-analysis was repeated separately for each stratum. In addition, the analysis was repeated in studies where manifest weight gain secondary to antipsychotic treatment was an inclusion criterion. The possible influence of publication bias was graphically evaluated by means of funnel plots where normalized dose reductions were plotted versus inverse standard error.

Statistical analyses were performed using StatsDirect statistical software version 2.7.2 (StatsDirect, Sale, Cheshire, UK) and MIX version 1.61 for Windows, October 2007 (Bax et al., 2006).

## Results

### Identification of studies

Figure 1 shows the flow of studies, from identification to final inclusion. A total of 195 citations were identified in the literature search. Of these, 17 studies were retrieved for detailed evaluation. Ten of the 17 studies were excluded for the following reasons: in three studies there was no metformin treatment (Assuncao et al., 2006; Deberdt et al., 2008; Weber and Wyne, 2006), three were open-label studies with no placebo group (Chen et al., 2008; Morrison et al., 2002; Shin et al., 2009), one study involved co-medication with sibutramine in the metformin group but not in the placebo group (Baptista et al., 2008), one was a small non-randomized single-blind cross-over study (Baptista et al., 2001), one article comprised the same patients as one of the included studies (Baptista et al., 2007b) and in one study all patients were treated with metformin and randomized to placebo or ondansatrone (Hoffmann et al., 2003). Seven studies fulfilled the inclusion criteria and were included in the final analysis (Arman et al., 2008; Baptista et al., 2006, 2007a; Carrizo et al., 2009; Klein et al., 2006; Wu et al., 2008a, b). Five studies were performed in adult patients (Baptista et al., 2006, 2007a; Carrizo et al., 2009; Wu et al., 2008a, b) and two in paediatric patients (Arman et al., 2008; Klein et al., 2006). In all seven studies, patients were exposed to atypical (as opposed to classical) antipsychotics, most commonly olanzapine. In one study the atypical antipsychotic medication was added to an established treatment with a classical depot antipsychotic (Baptista et al., 2006).

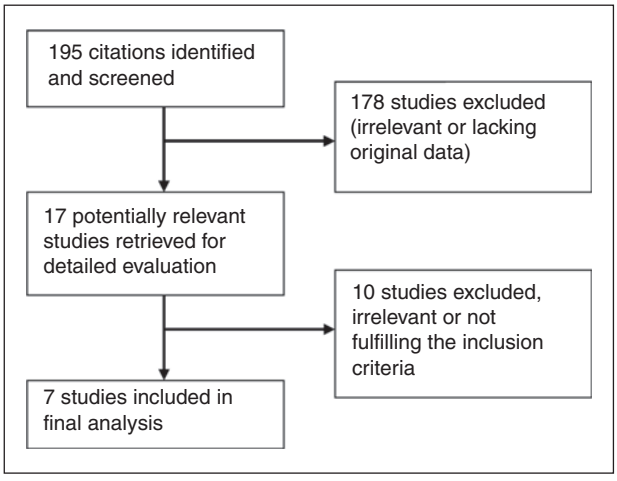


**Figure 1.** Flow diagram showing the number of citations identified, retrieved and included in final analysis.

One of the included studies (Wu et al., 2008b) presented results from four groups based on pharmacological treatment (metformin or placebo) and the administration of a psychoeducational/dietary/exercise programme (yes or no). In the meta-analysis, this study was treated as two separate comparisons between metformin and placebo, one in patients exposed to the programme and one in unexposed patients.

Table 1 presents the characteristics of the five studies included in the meta-analysis comprising adult patients (one study (Wu et al., 2008b) is subdivided as described above). All studies were published between 2006 and 2009. Two studies were performed in Asia and three in South America. A total of 328 patients were included in the five studies, 254 of whom were already receiving treatment with atypical antipsychotics at the time of inclusion, and the mean follow-up time was 12.6 weeks. The mean age of the patients was 35 years, the mean body weight at the time of inclusion was 66 kg, and mean body mass index (BMI) was 24.8.

Table 2 presents the characteristics of the two studies comprising paediatric patients. A total of 70 paediatric patients with a mean age of 11.7 years were included in the two studies and the mean follow-up time was 14.2 weeks. Mean BMI differed widely between the two studies (17.2 versus 27.8). However, BMI is not considered to be a good marker for overweight in paediatric populations, where age-adjusted BMI percentiles should preferably be used (Mei et al., 2002).

## *Meta-analysis*

A forest plot of the meta-analysis in adult patients is presented in Figure 2. Based on a random-effects model, 12–14 weeks of metformin treatment caused a significant weight reduction compared with placebo ($p < 0.001$). The mean difference in weight change between the two groups amounted to 4.8% of the body weight (95% CI 1.6 to 8.0). In children, the corresponding value was slightly lower at 4.1% (95% CI 2.2 to 6.0).

## *Sensitivity analyses*

There was evidence of a substantial between-studies heterogeneity in the overall meta-analysis (Cochran $Q$ test $p < 0.0001$, $I^2 = 92\%$), and possible sources of this heterogeneity were investigated in subgroup analyses (Figure 3). There was a pronounced difference between the metformin-induced weight change in studies comprising adult Asian patients (Wu et al., 2008a, b), −7.8% (95% CI −4.4 to −11.2), compared with studies comprising adult, mainly Hispanic patients (Baptista et al., 2006, 2007a; Carrizo et al., 2009), −2.0% (95% CI −0.7 to −3.3). Dividing the studies into those where metformin was provided from the onset of treatment with atypical antipsychotics (Baptista et al., 2006; Wu et al., 2008a) and those where metformin was given to patients stabilized on atypical antipsychotics (Baptista et al., 2007a; Carrizo et al., 2009; Wu et al., 2008b) had no discernable impact on the results. In the former group, metformin was associated with a non-significant weight change of −4.8% (95% CI −12.3 to 2.6) and in the latter group with a change of −4.8% (95% CI −8.7 to −1.0). When the analysis was further restricted by only including patients with a manifest weight increase (>10%) while receiving atypical antipsychotics (Wu et al., 2008b) (this study was divided into two studies as mentioned above), the weight-reducing effect of metformin treatment increased to 7.5% (95% CI 2.9 to 12).

**Table 1.** Characteristics of included studies in adult patients

| Reference | Country | Men | Age (years) | BMI | Follow-up (weeks) | Antipsychotic | Metformin | | | Placebo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *n* | Mean* | SD | *n* | Mean* | SD |
| Baptista et al. (2006) | Venezuela | 51.4% | 47.7 | 23.1 | 14 | O | 19 | 9.43% | 5.66% | 18 | 10.61% | 3.87% |
| Baptista et al. (2007a) | Venezuela | 58.4% | 44.1 | 25.6 | 12 | O | 36 | −2.11% | 4.83% | 36 | −0.27% | 4.27% |
| Carrizo et al. (2009) | Venezuela | 79.6% | 38.9 | 28.0 | 14 | C | 24 | −2.3% | 3.5% | 30 | 0.2% | 3.8% |
| Wu et al. (2008a) | China | 54.1% | 25.1 | 21.4 | 12 | O | 18 | 3.41% | 4.88% | 19 | 12.16% | 7.49% |
| Wu et al. (2008b) +LSI | China | 50.0% | 26.3 | 24.6 | 12 | C, O, R, S | 32 | −7.28% | 4.94% | 32 | −2.16% | 2.78% |
| Wu et al. (2008b) −LSI | China | 50.0% | 26.3 | 24.5 | 12 | C, O, R, S | 32 | −4.95% | 3.00% | 32 | 4.80% | 3.00% |

Quantitative study characteristics are presented as mean values.
BMI: body mass index, C: clozapine, LSI: life style intervention, ND: no data presented, O: olanzapine, R: risperidone, S: sulpiride, SD: standard deviation.
* Mean difference in body weight change from baseline.

**Table 2.** Characteristics of included studies in paediatric patients

| Reference | Country | Men | Age (years) | BMI | Follow-up (weeks) | Antipsychotic | Metformin | | | Placebo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *n* | Mean* | SD | *n* | Mean* | SD |
| Arman et al. (2008) | Iran | 65.6% | 10.1 | 17.2 | 12 | R | 16 | 2.70% | 1.58% | 16 | 6.42% | 4.04% |
| Klein et al. (2006) | US | 55.3% | 13.1 | 27.8 | 16 | O, R, Q | 18 | −0.19% | 4.25% | 20 | 5.40% | 8.38% |

Quantitative study characteristics are presented as mean values.
BMI: body mass index, O: olanzapine, Q: quetiapine, R: risperidone, SD: standard deviation.
* Mean difference in body weight change from baseline.

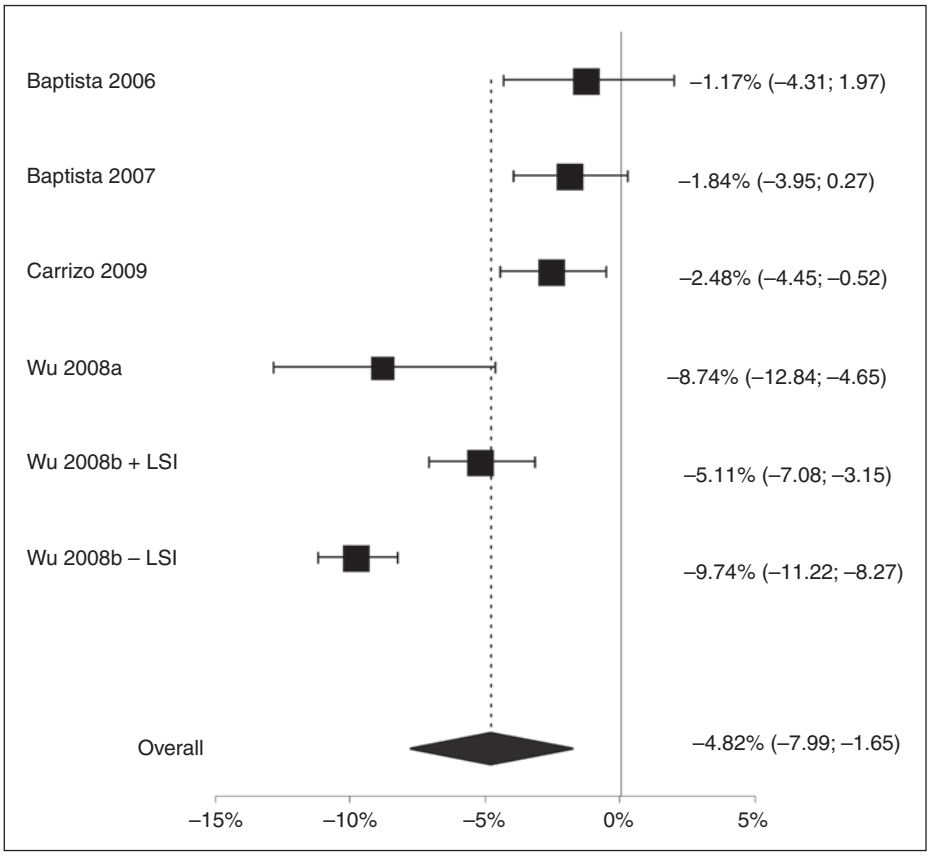


**Figure 2.** Forest plot of placebo-adjusted body weight change during metformin treatment in adult patients exposed to atypical antipsychotics. Brackets denote 95% confidence intervals. LSI, lifestyle intervention.

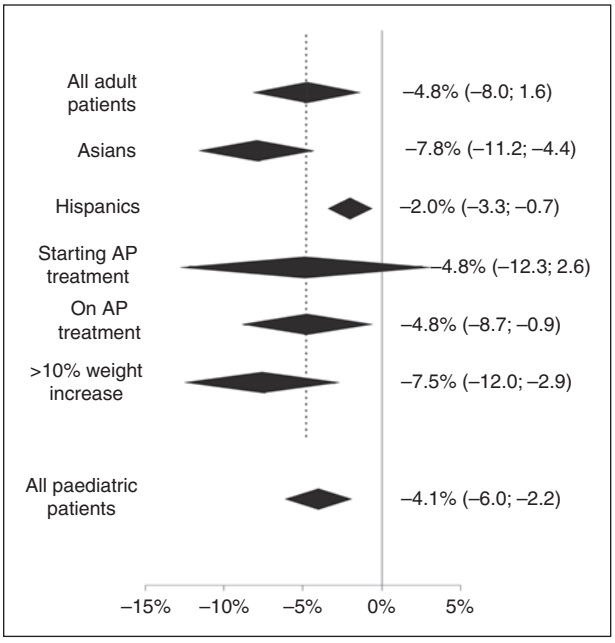


**Figure 3.** Placebo-adjusted weight changes (95% confidence intervals) in subgroups of antipsychotic-exposed patients treated with metformin. The dotted line indicates the effect size in the overall analysis (all adult studies).

### *Publication bias*

A funnel plot of the studies included in the overall analysis (studies in adults) is presented in Figure 4. Although it confirms the presence of heterogeneity, there is no evidence of a bias towards selective publication of favourable results. On the contrary, the largest metformin effect was observed in the study with the highest level of precision, opposite to the pattern typically associated with such publication bias. Similar funnel plots of the studies included in the subgroup analyses were not suggestive of publication bias (data not shown).

## Discussion

In this systematic review and meta-analysis we demonstrate that metformin treatment induces weight loss and prevents weight gain in non-diabetic patients taking atypical antipsychotic drugs. The mean weight change in metformin-treated patients compared with placebo-treated patients was −4.8 % of the initial body weight in adults and −4.1% in children. These might be considered as rather moderate effects and could preferably be achieved by lifestyle changes. In reality, average weight reductions of this magnitude or larger are often difficult to achieve, and in patients suffering from psychotic diseases lifestyle changes might be especially difficult to manage. In addition, metformin may have favourable impact

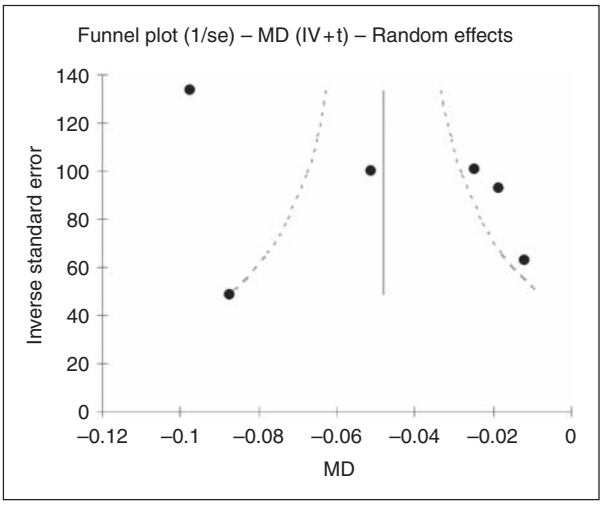


**Figure 4.** Funnel plot of observed effect sizes in individual adult studies plotted against inverse standard error.

on blood glucose levels and other metabolic parameters exceeding those achievable by lifestyle changes alone.

In a large meta-analysis the drugs orlistat and sibutramine, both approved for weight reduction, reduced body weight by only 2.9% and 4.3%, respectively (Rucker et al., 2007).

Although all published randomized trials of metformin for weight reduction or decreased weight gain in patients treated with atypical antipsychotics presented point estimates in favour of a beneficial effect, there was considerable heterogeneity among studies regarding the effect size. One source of heterogeneity was the selective inclusion of patients with a manifest weight gain in one large study (Wu et al., 2008b). This elimination of patients in whom the antipsychotic treatment had little effect on body weight could increase the apparent effect of metformin, as confirmed in the sensitivity analysis.

In this meta-analysis, the beneficial effects of metformin were strikingly more pronounced in Asian patients than in Hispanic patients. Although this could be due to genetic and environmental effects, differences in the designs of the included studies could also have contributed. For example, the majority of Asian patients included in the meta-analysis had a manifest weight gain at the time of inclusion. Since manifest weight gain was identified as a predictor of favourable treatment outcome, this could have contributed to the observed influence of ethnicity. Differences in lifestyle intervention programmes could also have contributed, although an incomplete description of the non-pharmacological interventions in some studies makes the comparison difficult. The importance of lifestyle interventions was demonstrated by Wu et al. in a randomized comparison of metformin versus placebo and lifestyle interventions versus no such interventions (Wu et al., 2008b). Although the combination of lifestyle intervention and metformin gave the most effective weight reduction, the marginal effect of metformin was actually reduced by the lifestyle intervention. In this study, metformin reduced body weight by almost 10% in patients without lifestyle interventions, while those who had already had the benefit of an intervention programme (in itself reducing body weight by 6%) only lost an additional 5% when treated with metformin.

The present study has several limitations. As it is a meta-analysis based on summary data from a limited number of studies, its precision is less than what could have been achieved in a single clinical trial with an equal number of included patients. In addition, the use of aggregated data makes it less easy to evaluate the influence of various patient characteristics on the response to metformin. The heterogeneity of the analysis results indicate that the included studies and/or study populations differed in ways that were of importance for the metformin effect. Some of these modifying factors (e.g. ethnicity and manifest weight gain) were identified in the sensitivity analysis, but other as yet unknown predictors of response may remain and would preferentially be investigated in individual-level datasets. To compensate for the heterogeneity, a random-effects model was used. This model provides considerably wider CIs than the fixed-effect model, but there may still be certain patient populations to whom the results do not apply, and future studies should aim at quantifying the metformin treatment effect in different well-defined patient populations treated with antipsychotics. Another limitation is the fact that some patients receiving metformin from the start of atypical antipsychotic therapy had received conventional antipsychotics prior to randomisation. Since these drugs could also cause body weight increase, the expected weight change associated with exposure to atypical antipsychotics could differ from that in patients previously unexposed to antipsychotics.

Although no severe adverse effects were reported in any of the studies, the rare but potentially lethal adverse reaction of lactic acidosis has to be taken into consideration. However, metformin-associated lactic acidosis is primarily seen in patients with renal insufficiency (Hundal and Inzucchi, 2003). Impaired renal function is not uncommon in the 'standard' metformin-treated patient, having diabetes and often being elderly. On the other hand, the typical patient on antipsychotic drugs is frequently young and physically healthier, and the risk of metformin-induced lactic acidosis is most likely lower in this group of patients. However, in a situation of temporary dehydration, for example after gastroenteritis, the risk of lactic acidosis is increased (Hundal and Inzucchi, 2003).

Moreover, recent findings suggest that metformin increases the generation of amyloid-beta species, involved in the pathogenesis of Alzheimer's disease (Chen et al., 2008). It is assumed by the authors of the article that metformin might contribute in this way to the development of Alzheimer's disease (Chen et al., 2009).

Metformin is not approved for use in non-diabetic patients, and it is not advisable to generally recommend metformin for weight reduction. Far from all patients experience an excessive body weight gain from antipsychotic agents, and a prophylactic treatment may not be justifiable. In those patients who experience a significant weight gain, however, the metformin effect may be even larger than that seen in the overall meta-analysis. As mentioned above, a subgroup analysis in these patients demonstrated a large metformin-associated weight loss of 7.5%. In addition, metformin may have additional positive effects on antipsychotic-induced hyperglycaemia and metabolic dysfunction, although this was not investigated in the current study.

Ongoing studies will bring more information to the field, for example the METS study ('The Use of Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia'). This multicentre study will randomize 80 inpatients on antipsychotic medication to metformin or placebo, and the trial is estimated to be completed in September 2009 (http://clinicaltrials.gov/ct2/show/related/NCT00816907).

Considering possible severe adverse reactions to metformin, an individualized risk–benefit analysis must always be performed before the drug is prescribed. Long-term studies in well-characterized patient populations are needed to elucidate whether metformin treatment is a safe and effective therapy for preventing weight gain in patients treated with antipsychotic agents, and to determine which patients benefit the most from such therapy.

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## Declaration of Conflicting Interests

The authors declare that they do not have any conflict of interest.

## Appendix

### *PubMed*

'Metformin' as MeSH or text word was combined with each of the following search phrases:

Antipsychotic agents, levomepromazine, flufenazin, perfenazine, prochlorperazine, haloperidol, melperone, sertindole, ziprasidone, flupenthixol, chlorprotixen, chlorprothixene, zuclopenthixol, clozapine, olanzapine, quetiapine, risperidone, aripiprazole, paliperidone, chlorpromazine, promazine, acepromazine, triflupromazine, dixyrazine, thiopropazate, trifluoperazine, acetophenazine, thioproperazine, butaperazine, perazine, periciazine, thioridazine, mesoridazine, pipothiazine, trifluperidol, moperone, pipamperone, bromperidol, benperidol, droperidol, oxipertine, molindone, clopenthixol, tiotixen, fluspirilene, pimozide, penfluridol, loxapine, tetrabenzaine, sulpiride, sultopride, tiapride, remoxipride, amisulpride, levosulpiride, prothipendyl, mosapramine, or zotepine.

### *EMBASE*

'Metformin' and 'body weight' as EMTREE entries was combined with each of the following search phrases:

Neuroleptic agent, levomepromazine, fluphenzine, perfenazine, prochlorperazine, haloperidol, melperone, sertindole, ziprasidone, flupenthixol, chlorprotixen, chlorprothixene, zuclopenthixol, clozapine, olanzapine, quetiapine, risperidone, aripiprazole, paliperidone, chlorpromazine, promazine, acepromazine, triflupromazine, dixyrazine, thiopropazate, trifluoperazine, acetophenazine, thioproperazine, butaperazine, perazine, periciazine, thioridazine, mesoridazine, pipothiazine, trifluperidol, moperone, pipamperone, bromperidol, benperidol, droperidol, oxipertin, molindone, clopenthixol, tiotixene, fluspirilene, pimozide, penfluridol, loxapine, tetrabenazine, sulpiride, sultopride, tiapride, remoxipride, amisulpride, levosulpiride, prothipendyl, mosapramine, or zotepine.

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