Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis
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CRD summary
The review concluded that metformin significantly reduced olanzapine-induced weight gain in the short term. There was a significant reduction in body mass index, but the reduction in waist circumference was not significant. Potential review limitations and uncertain study quality make the reliability of the authors’ conclusions unclear.

Authors' objectives
To evaluate the effectiveness of metformin for reducing or preventing olanzapine-induced weight gain.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for publications in English; search terms were reported. Search dates were not explicitly stated, but the included studies were published between 2006 and 2008. Bibliographies of retrieved articles and relevant reviews were handsearched.

Study selection
Randomised double-blind controlled trials (RCTs) that compared metformin with placebo for olanzapine-induced weight gain were eligible for inclusion. Minimum duration was 12 weeks. Primary outcomes were body weight, waist circumference and body mass index (BMI). Studies that used metformin in combination with other drugs were excluded. Open label studies were excluded.

Olanzapine dose ranged from 5mg to 20mg. Metformin dose ranged from 750mg/day to 2,550mg/da. Control groups used olanzapine plus placebo. Two studies were of prophylactic treatment and two were of patients already with weight gain. All studies included patients with schizophrenia, two studies included only schizophrenia patients, one study included patients with schizoaffective disorder and one study included patients with bipolar disorder.

One reviewer selected abstracts and further selection was made by two independent reviewers; disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
Methodological quality was assessed using the five-point Jadad scale of randomisation, double-blinding and description of withdrawals and drop-outs.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
Continuous data were extracted as mean differences with standard deviations and 95% confidence intervals (CI) using a standardised form.

The authors did not report how many reviewers performed data extraction.

Methods of synthesis
Mean differences were pooled using a fixed-effect model to give weighted mean differences (WMD) with 95% CIs. Between-study heterogeneity was determined using Cochrane's Q test and the $I^2$ statistic. Where $I^2$ was more than 50% (moderate heterogeneity), a DerSimonian-Laird random-effects model was used for the meta-analysis. There were too few studies to assess publication bias.

Results of the review
Four double-blind RCTs were identified (224 participants, range 40 to 80). Two studies were randomly assigned in blocks of four/eight. Allocation concealment was adequately described in two studies. Drop-out ranged from 7.5% to 10%. Follow-up was for 12 weeks in three studies and 14 weeks in the fourth study. All four studies contributed to the meta-analyses.
Weight gain was significantly lower for metformin versus placebo (WMD -5.02kg, 95% CI -6.10 to -3.93, \( I^2 = 0\)%, fixed-effect model). Waist circumference was lower for the metformin group than placebo, but the effect was not significant (WMD -1.42cm, 95% CI -3.13 to 0.29, \( I^2 = 85\)%, random-effects model). BMI was significantly lower for metformin versus placebo (WMD -1.82kg/m\(^2\), 95% CI -2.19 to -1.44, \( I^2 = 0\)%, fixed-effect model). Adverse events were similar between groups.

**Authors' conclusions**

Present evidence suggested that short-term modest weight loss was possible with metformin in patients with olanzapine-induced weight gain.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched, but only two databases were used when a more extensive search may have been more effective. It was unclear whether there were restrictions on language and publication status. Publication bias was not assessed due to the small number of studies. Study quality was assessed, but the reporting was not comprehensive. The initial study selection process was conducted by only one reviewer and it was not clear whether efforts were made to reduce error and bias in other aspects of the review process.

Some relevant study details were reported but, for example, little detail was provided on the age and gender of patients, which would have been relevant for this study. Statistical heterogeneity was assessed. There was evidence for heterogeneity with one outcome. The statistical method used for the meta-analysis of the RCTs seemed appropriate. No sensitivity analyses were performed, yet the authors concluded that metformin was not indicated for prophylaxis but was following weight gain.

Potential limitations in the review process and uncertain study quality make the extent to which the authors’ conclusions are reliable unclear.

**Implications of the review for practice and research**

**Practice:** The authors advised that patients should be screened at baseline and monitored at the commencement of antipsychotic treatment for emerging metabolic effects, including significant weight gain, in which case the risks and benefits of antipsychotic choice and concomitant medications should be re-evaluated. Metformin may not be routinely indicated for patients as prophylaxis, but its use may be justified in patients with olanzapine-induced weight gain when there are no contraindications to metformin.

**Research:** The authors identified a need for further studies in more homogenous populations on the potential use of metformin in assisting olanzapine-treated patients in the long-term control of body weight and BMI. Studies should use valid methods for measuring and reporting outcomes. The authors suggested the use of binary outcomes.

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