Efficacy of rosiglitazone and pioglitazone compared to other anti-diabetic agents: systematic review and budget impact analysis
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Authors' objectives
To evaluate the effectiveness of rosiglitazone and pioglitazone compared with other oral antidiabetic agents in the treatment of type 2 diabetes.

Searching
MEDLINE, EMBASE, HealthSTAR, Pascal, SciSearch and TOXLINE (all from 1990 to 2001) and the Cochrane Library (Issue 3, 2002) were searched for studies published in English and other languages. Database updates and alerts were set up on Adis LMS Drug Alerts, Current Contents Search, EMBASE Alert, MEDLINE, Pascal, Pharmaceutical News Index and SciSearch. Additional searches were performed in the websites of regulatory agencies, health technology assessment and near-health technology assessment agencies, trial registries, and in other specialised databases. The search terms used were given in the report. The bibliographies of retrieved studies were checked, and the manufacturers of pioglitazone and rosiglitazone were contacted to obtain product monographs and were invited to submit other relevant information.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of rosiglitazone or pioglitazone used as monotherapy, or as add-on therapy to a non-thiazolidinedione drug, were eligible for inclusion. Non-thiazolidinedione drugs included alpha-glucosidase (acarbose), biguanides (metformin), carbamoyl benzoic acid derivatives or meglitinides (repaglinide) and sulphonylureas (chlorpropamide, gliclazide, glyburide, tolbutamide). Studies of add-on treatment with insulin were also eligible. Details of the intervention and control in all included studies were reported in the review.

Participants included in the review
Studies of adults aged 18 years or older with type 2 diabetes requiring drug treatment were eligible for inclusion. Demographic details were not reported in the review.

Outcomes assessed in the review
The primary outcomes of interest were fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c). The secondary outcomes were:

- serum lipid profiles, i.e. total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, or triglyceride;
- haematological parameters such as haemoglobin or haemocrit;
- liver function tests, i.e. alanine aminotransferase or aspartate aminotransferase;
- hypoglycaemia (severity and withdrawals); and
- other relevant parameters such as weight, blood-pressure (diastolic and systolic), or oedema.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies for inclusion.
Assessment of study quality
The authors assigned a quality score to each study (1 being the lowest and 5 the highest), using the Jadad instrument to assess randomisation, blinding and withdrawals. Allocation concealment was rated as adequate, unclear or inadequate for each individual study. Two reviewers independently assessed the validity of each individual study.

Data extraction
Two reviewers independently extracted the data from individual studies and resolved any disagreements by discussion.

Intention-to-treat data on the mean difference and standard deviation were extracted for each outcome of interest. If the data required were not presented in the report, or they were not presented in SI units, methods were used to compute the required data or authors were contacted for additional information.

Methods of synthesis
How were the studies combined?
Where sufficient data were available, the studies were pooled in a meta-analysis for each outcome of interest, using a random-effects model. A pooled weighted mean difference (WMD) with 95% confidence interval (CI) was calculated separately for rosiglitazone and pioglitazone for each outcome of interest. Studies that could not be pooled were presented alongside the pooled estimate in a narrative discussion.

How were differences between studies investigated?
A chi-squared test was used to assess statistical heterogeneity using a significance level of P equal to 0.1.

Results of the review
Nineteen RCTs (n=4,396) were included in the review.
Rosiglitazone (11 RCTs, n=2,701).
Most of the trials were of a poor quality: two scored 4 out of a possible 5, while the rest scored 1 or 2.
Glycaemic control.
Rosiglitazone monotherapy was associated with a statistically significant decrease in FPG (WMD -0.62, 95% CI: -1.07, -0.17, P=0.007), based on 507 patients in 2 RCTs (one versus glyburide and one versus repaglinide). There was no evidence of statistical heterogeneity (P=0.93). No significant difference in HbA1c was found between rosiglitazone monotherapy and control (WMD -0.08, 95% CI: 0.65, 0.49, P=0.8), based on 507 patients in the same 2 RCTs. There was evidence of statistical heterogeneity (P=0.01).
Add-on therapy with rosiglitazone was associated with a statistically significant decrease in FPG (WMD -2.82, 95% CI: -3.15, -2.48, P=0.00001), based on 1,890 patients in 7 RCTs. There was evidence of statistical heterogeneity (P=0.09). Add-on therapy with rosiglitazone was also associated with a statistically significant reduction in HbA1c (WMD -1.29, 95% CI: -1.37, -1.22, P<0.00001), based on 1,907 patients in 8 RCTs. There was no evidence of statistical heterogeneity (P=0.74).
Secondary outcomes.
Compared with other antidiabetic therapy, rosiglitazone was associated with a significant increase in total cholesterol, LDL-cholesterol and HDL-cholesterol levels. No significant difference was found in the levels of triglycerides. Most studies reported normal levels of liver enzymes and no serious adverse effects on liver function were reported. Rosiglitazone was associated with a small decrease in haemoglobin and haemocrit. Hypoglycaemic events were mild to moderate in severity, and were more frequent in patients given add-on therapy than rosiglitazone monotherapy. Hypoglycaemia was most common in patients given rosiglitazone combined with insulin. Rosiglitazone was associated with a weight gain of 0.7 to 5.3 kg, depending on dose and combination regimen used, and a mild hypotensive effect was reported. Oedema occurred in 2.5 to 3.5% of patients given rosiglitazone monotherapy, 10.8% of patients given
rosiglitazone combined with gliclazide, and 13.1 to 16.2% of patients given rosiglitazone combined with insulin.

Pioglitazone (8 RCTs, n=1,695). Most of the trials were of a poor quality: one scored 3 out of 5, seven scored 2, and one scored 1.

Glycaemic control.

Pioglitazone was associated with a statistically significant increase in HbA1c (WMD 0.46, 95% CI: 0.03, 0.9, P=0.04) compared with glyburide or repaglinide, based on 141 patients in 2 RCTs. There was no evidence of statistical heterogeneity (P=0.59). No significant difference was found in FPG levels between pioglitazone monotherapy and repaglinide (WMD 0.89, 95% CI: -0.26, 2.04, P=0.13), based on 123 patients in 1 RCT.

Add-on therapy with pioglitazone was associated with a statistically significant reduction in HbA1c compared with continuing non-thiazolidinedione monotherapy (WMD -1.29, 95% CI: -1.6, -0.99, P<0.00001), based on 1,422 patients in 6 RCTs. There was evidence of statistical heterogeneity (P=0.0002). Add-on therapy with pioglitazone was also associated with a statistically significant decrease in FPG compared with monotherapy with other diabetic agents (WMD -2.87, 95% CI: -3.59, -2.15, P<0.00001), based on 1,052 patients in 5 RCTs. There was evidence of statistical heterogeneity (P=0.0006).

Secondary outcomes.

Compared with other antidiabetic therapy, pioglitazone was associated with a statistically significant greater increase in HDL-cholesterol levels and a decrease in triglyceride levels. No significant difference was found for levels of total cholesterol or LDL-cholesterol. Most studies reported normal levels of liver enzymes and no serious adverse effects on liver function were reported. Pioglitazone was associated with a small decrease in haemoglobin and haemocrit. Pioglitazone monotherapy was not frequently associated with hypoglycaemia; occurrence increased when used in combination with other antidiabetics, most notably when combined with insulin. Pioglitazone was associated with a weight gain ranging from 0.95 to 3.6 kg, depending on the dose and combination regimen used, and a small decrease in systolic blood-pressure was reported. Oedema was frequently reported and was highest in patients given pioglitazone combined with insulin.

Cost information

The authors conducted a budget impact analysis to determine the impact on oral antidiabetic expenditure if rosiglitazone and pioglitazone were added to public-funded drug plans in Canada. The analysis found that national net expenditure would increase by between $11.8 million and $88.5 million, depending on the uptake and number of patients treated.

Authors' conclusions

Based on a small number of trials, rosiglitazone and pioglitazone monotherapy have effects on glycaemic control that are comparable with other antidiabetic agents. Combination therapy produces significantly greater effects on glycaemic control than continuing therapy with other antibiotic therapy alone. Both drugs appear to be well tolerated, although further studies are needed to evaluate their long-term safety.

CRD commentary

The review question was clear and the inclusion criteria appear appropriate. Extensive searches were performed to identify published and unpublished studies and no language restrictions were applied, thus minimising the possibility of publication and language bias. Methods were used to minimise bias and error in the study selection and data extraction processes. The validity of the included studies was assessed systematically and the results were reported.

Adequate details of each included study were presented in the report, and the methods used to combine the studies appear appropriate. Statistical heterogeneity was formally assessed and discussed in the interpretation of the results. In the analysis of rosiglitazone and pioglitazone as add-on therapy, the clinical diversity of the trials was not explored and the statistical heterogeneity identified, particularly in the analysis of pioglitazone, means that the positive treatment
effects can only be considered tentative. This was a well-conducted and reported systematic review, which provides assurance that the conclusions are reliable.

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

Practice: The authors stated that rosiglitazone or pioglitazone combination therapy with other antidiabetic agents is effective at improving glycaemic control in patients with type 2 diabetes who are not controlled by a single therapy. In addition, the authors highlighted that Health Canada and the U.S. Food and Drug Administration have issued safety reminders regarding the risk of both agents in patients with heart failure.

Research: The authors stated that studies of longer duration are needed to evaluate the effect of rosiglitazone and pioglitazone on the development of diabetic complications and long-term safety.

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