Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes
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CRD summary
This review assessed different classes of non-insulin antidiabetic drugs, given alongside metformin therapy, in patients with type 2 diabetes mellitus not controlled by metformin alone. The authors concluded that all classes of drug were associated with similar glycated haemoglobin A$_1c$ reductions, but differed in their associations with weight gain and risk of hypoglycaemia. These conclusions are likely to be reliable.

Authors’ objectives
To determine the comparative efficacy, risk of weight gain, and hypoglycaemia associated with non-insulin antidiabetic drugs in patients with type 2 diabetes mellitus not controlled by metformin alone.

Searching
MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to January 2010; search terms were reported. Reference lists of reports of clinical trials and review articles were also searched manually. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared a non-insulin antidiabetic drug with either placebo or another non-insulin antidiabetic drug, given alongside metformin therapy, for patients with type 2 diabetes mellitus and an inadequate response to stable metformin monotherapy, were eligible for inclusion. Stable metformin therapy was defined as at least 1,500mg per day, or the maximum tolerated dose (of at least 1g per day), maintained for at least four weeks. Patients had to be treated for between 12 and 52 weeks from randomisation and the outcomes of glycated haemoglobin (HbA$_1c$) had to be reported for trials to be eligible for inclusion.

The average age of participants in the included trials ranged from 53 to 62 years and between 23% and 75% of participants were male. The average baseline HbA$_1c$ ranged from 6.4% to 9.3%. The classes of antidiabetic drug assessed by the included trials were sulphonylureas, glinides, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, and glucagon-like peptide 1 (GLP-1) analogues. Details of specific drugs and dosages were presented in an online supplementary table.

Two authors independently selected the trials.

Assessment of study quality
The quality of the trials was assessed using the Jadad scale, which assesses randomisation, blinding, and withdrawals; trials scoring less than three out of five were considered to be of low methodological quality.

Two reviewers independently assessed the quality of the included trials and disagreements were resolved through discussion.

Data extraction
The mean differences between treatment groups in change from baseline to follow-up were calculated for the continuous outcomes HbA$_1c$ and body weight, along with 95% confidence intervals. When the variances for net changes were not reported directly, they were calculated from confidence intervals, p values, or individual variances. When the variance for paired differences was not reported, they were calculated from variances at baseline and at the end of follow-up. Relative risks were calculated for the dichotomous outcomes of achievement of HbA$_1c$ goal of less than 7% and occurrence of hypoglycaemic events, along with 95% confidence intervals. Trial authors were contacted for clarification or additional data when necessary.
Two reviewers independently extracted data from the included trials and disagreements were resolved through discussion.

**Methods of synthesis**

Separate analyses were conducted for each class of oral antidiabetic drug. A DerSimonian and Laird random-effects model was used to calculate the weighted mean differences, along with 95% confidence intervals, for continuous outcomes, and weighted relative risks, along with 95% confidence intervals, for dichotomous outcomes. Heterogeneity was assessed using the $I^2$ statistic.

A mixed-treatment comparison meta-analysis was conducted to compare the different drug treatment classes, using a Bayesian Markov chain Monte Carlo method. A random-effects model was used to calculate weighted mean differences for continuous outcomes and weighted relative risks for dichotomous outcomes for all treatments relative to placebo, with accompanying 95% credible intervals. The residual deviance was calculated for each outcome. The degree of coherence between mixed-treatment comparison and traditional meta-analysis results was assessed through a qualitative comparison of the results for each matched drug-to-drug comparison derived from both meta-analytic methods.

Subgroup analyses were performed to assess the effect of the baseline disease severity and duration of the trial on the change in HbA$_{1c}$ endpoint. Sensitivity analyses were performed to assess the effect of trial quality on the change in HbA$_{1c}$ endpoint. Publication bias was assessed using funnel plots and the Egger weighted regression statistic.

**Results of the review**

Twenty-seven RCTs were included in the review (11,198 participants). The majority of trials scored three or four out of five for quality, only two trials scored less than three out of five and were considered to be of low methodological quality.

**Change in HbA$_{1c}$:** All classes of antidiabetic drug were associated with statistically significant reductions in HbA$_{1c}$ in both traditional and mixed-treatment comparison meta-analyses. The mixed-treatment comparison showed the following reductions in HbA$_{1c}$: sulphonylureas 0.79% (95% CrI 0.62 to 0.97), glinides 0.65% (95% CrI 0.36 to 0.97), thiazolidinediones 0.85% (95% CrI 0.66 to 1.08), α-glucosidase inhibitors 0.64% (95% CrI 0.26 to 1.03), DPP-4 inhibitors 0.78% (95% CrI 0.64 to 0.93), and GLP-1 analogues 0.97% (95% CrI 0.65 to 1.30).

**Achievement of HbA$_{1c}$ goal:** All classes of antidiabetic drug were associated with statistically significant increases in achievement of the HbA$_{1c}$ goal compared with placebo, in both traditional and mixed-treatment comparison meta-analyses. The mixed-treatment comparison showed the following relative risks for achieving the HbA$_{1c}$ goal: sulphonylureas 2.49 (95% CrI 1.95 to 3.32), glinides 2.25 (95% CrI 1.48 to 3.90), thiazolidinediones 2.71 (95% CrI 1.74 to 3.80), DPP-4 inhibitors 2.51 (95% CrI 2.04 to 3.22), and GLP-1 analogues 3.20 (95% CrI 2.01 to 6.24). There were insufficient data to evaluate α-glucosidase inhibitors for this outcome.

**Change in body weight:** Three classes of antidiabetic drug were associated with statistically significant increases in body weight compared with placebo in the mixed-treatment comparison; sulphonylureas 2.06kg (95% CrI 1.15 to 2.96), glinides 1.77kg (95% CrI 0.46 to 3.28), and thiazolidinediones 2.08kg (95% CrI 0.98 to 3.17). GLP-1 analogues were associated with a significant decrease in body weight compared with placebo (-1.74kg; 95% CrI -3.11 to -0.48). There was no statistically significant weight change associated with α-glucosidase inhibitors nor DPP-4 inhibitors.

**Hypoglycaemia:** Two classes of antidiabetic drug were associated with an increased risk of hypoglycaemia compared with placebo in the mixed-treatment comparison; sulphonylureas 4.57 (95% CrI 2.11 to 11.45) and glinides 7.50 (95% CrI 2.12 to 41.52).

The results of mixed-treatment comparison meta-analyses and traditional meta-analyses were consistent for each of the outcomes. The results of subgroup analyses and sensitivity analyses were also presented. Funnel plots and the Egger weighted regression statistic suggested a low likelihood of publication bias.
Authors' conclusions

All classes of non-insulin antidiabetic drug, when added to maximal metformin therapy, were associated with similar HbA1c reductions, but they differed in their associations with weight gain and risk of hypoglycaemia.

CRD commentary

This review addressed a clear question and was supported by appropriate inclusion criteria. Adequate attempts were made to identify relevant studies, with no language restrictions, reducing the potential for language and publication bias. The likelihood of publication bias was assessed and found to be low. Two reviewers independently undertook trial selection, data extraction, and validity assessment procedures, reducing the potential for reviewer bias and error. Validity was assessed, using published criteria, and the results were presented in supplementary online tables and used in the sensitivity analyses. Appropriate methods appear to have been used to pool the trials, although most of the analyses were based on only two or three trials and there was significant statistical heterogeneity in a few of the meta-analyses. Sensitivity and subgroup analyses were conducted in an attempt to investigate heterogeneity.

This was a well-conducted systematic review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that differences between drug classes, in terms of body weight change and rates of hypoglycaemia, should be taken into account when selecting a second-line treatment to add to stable maximum metformin therapy for type 2 diabetes mellitus, not controlled by metformin alone. They also stated that in addition to the efficacy and safety aspects evaluated by this review, contraindications (e.g. heart failure and renal dysfunction), other adverse effects (e.g. bone fracture, pancreatitis, and cardiovascular, gastrointestinal, and renal dysfunction), other therapeutic benefits (e.g. pleiotropic effects), or cost may guide the selection of therapy.

Research: The authors stated that future studies should report the associations between weight gain or loss on serum lipids or blood pressure.

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