Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis

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CRD summary
The review concludes that in combination with metformin, sulphonylureas and α-glucosidase inhibitors have similar levels of efficacy in reducing glycosylated haemoglobin A1 levels in patients with type 2 diabetes. The findings should be interpreted with caution given concerns about the reliability of the review methods and data.

Authors' objectives
To compare various hypoglycemic drugs as add-on treatments to metformin versus other oral monotherapies for type 2 diabetes.

Searching
MEDLINE was searched in January 2007 with no date restrictions using keyword search terms (terms reported). The reference lists of retrieved articles were searched for additional citations of interest. Only English language studies published in full were considered.

Study selection
Eligible studies were parallel or crossover randomised controlled trials (RCTs) that compared any hypoglycemic drug with placebo or another active drug in patients with type 2 diabetes who have failed to respond to previous therapy with metformin or another oral hypoglycemic agent. Treatment regimens had to last a minimum of 16 weeks. Studies where treatments lasted more than 36 weeks had to report glycosylated haemoglobin A1 (HbA1c) levels at 24 weeks (+/-4 weeks). Studies were excluded if patients were treated with more than one agent in combination with metformin.

Included studies assessed sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones, glinides and GLP-1 agonists. The majority of trials compared interventions to placebo. The remainder compared different sulphonylureas, insulins or glinides, or compared thiazolidinediones or insulins with sulphonylureas. Treatment durations ranged from 16 to 52 weeks. Patient ages ranged from 51.6 to 62.4 years.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For each included study the mean and variance of the control and experimental arms were extracted. The authors stated neither how the data were extracted for this review nor how many reviewers performed the data extraction.

Methods of synthesis
Meta-analysis was performed using the Hedges and Olkin method to calculate an effect size and 95% confidence interval (CI) for each study. Between-group comparisons were made using analysis of variance (ANOVA) methods incorporating baseline HbA1c (mean of active and comparator groups) as a covariate. A further analysis was performed based on trials of patients who failed metformin monotherapy.

Results of the review
Twenty-seven RCTs (n= 7,890) were included in this review: 16 placebo-controlled trials (n=3,743) and 11 active comparison trials (n=4,147).

Placebo-controlled trials. The 16 trials in this section of the review looked at: sulphonylureas (five trials); α-glucosidase inhibitors (five trials); thiazolidinediones (three trials); glinides (two trials); and GLP-1 agonists (one trial). After
adjusting for baseline HbA1c and when compared with placebo, sulphonylureas achieved a significantly greater reduction in HbA1c levels than did thiazolidinediones. None of the other intra-drug comparisons were statistically significant.

When only patients failing metformin monotherapy were included, there was no significant difference in the performance of sulphonylureas as against α-glucosidase inhibitors; no other statistical comparisons were possible.

Active comparison trials. The 11 trials in this section compared: thiazolidinediones and sulphonylureas (four trials); insulin and sulphonylureas (two trials); efficacy of agents within the same drug classes (two trials); premixed insulin with basal insulin analogues (two trials); and pioglitazone and a dual PPARα/γ activators (only one trial; not included in the analysis). Direct comparisons reported that sulphonylureas were significantly superior to thiazolidinediones in reducing HbA1c levels, 0.17 (95% CI: 0.16, 0.18, p<0.05). No significant differences were reported between insulin and sulphonylureas.

Authors' conclusions
When combined with metformin as add-on treatments, sulphonylureas and α-glucosidase inhibitors have similar levels of efficacy in reducing HbA1c levels.

CRD commentary
This review answered a clear research question, but by only including studies published in English the review may be at risk from publication and language bias. The authors also fail to report their methods in detail, which makes it difficult to assess the risk of reviewer error and bias. Not only the lack of any assessment of study quality but also the failure to report the level of heterogeneity between studies makes it difficult to assess the reliability of the data. The authors' conclusions in some cases rely on unadjusted indirect comparisons based on placebo-controlled data, which again suggests that the data may not be reliable (although some findings are confirmed in trials making direct comparisons between different drugs). In some cases the authors themselves advise caution due a lack of comparative data. Overall, given concerns about the potential for bias in the review methods and the questionable validity of the data, the findings of the review may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that α-glucosidase inhibitors and glinides should be considered alongside insulin, sulphonylureas and thiazolidinediones for the treatment of diabetes type 2 when metformin monotherapy has failed.

Research: The authors stated that further RCTs are required comparing different agents in combination with metformin to facilitate the formation of treatment algorithms.

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