Glycaemic control and adverse events in patients with type 2 diabetes treated with metformin + sulphonylurea: a meta-analysis

Belsey J, Krishnarajah G

CRD summary
This review of that adding sulphonylureas to the treatment of patients with type 2 diabetes not controlled by metformin would reduce glycated haemoglobin by no more than 1% and may increase side-effects. Despite poor reporting of some aspects of the review process, the conclusions reflected the results of the review and appear likely to be reliable.

Authors' objectives
To quantify the effect of a sulphonylurea on glycaemic control and the risk of adverse events when incorporated into the treatment regimen of patients with type 2 diabetes inadequately controlled by metformin.

Searching
PubMed, EMBASE and The Cochrane Library were searched and Google Scholar used to find studies. Search terms were reported. Search dates were not reported. Reference lists of identified papers were searched. Handsearches of nine journals from the previous 20 years were conducted. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) in patients with type 2 diabetes and whose glycaemic control was inadequate following a run-in period on maximal metformin monotherapy were eligible for inclusion. At least one treatment arm had to be metformin and sulphonylurea. There had to be at least 50 patients per arm. RCTs had to be of at least 12 weeks duration and to report glycated haemoglobin and/or fasting plasma glucose at baseline and completion.

Participants in included studies had a baseline glycated haemoglobin of 6.42% to 8.53% and fasting plasma glucose of 8.65 to 11.3mmol/L. The sulphonylurea treatment was glimepiride (1 to 6mg/day), glipizide (5 to 20mg/day), gliclazide (80 to 320mg/day) and glibenclamide (2.5 to 20mg/day). The comparator treatments were metformin alone (500 to 2,250mg/day) and in combination with sitagliptin (100mg/day), nateglinide (180 to 540mg/day), rosiglitazone (4mg/day) and pioglitazone (15 to 45mg/day).

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

Assessment of study quality
Each study was assessed using the Jadad scale for randomisation, blinding and loss to follow-up. Assessment was by two reviewers working independently, with a third reviewer to adjudicate if there was disagreement. Only studies that scored 3 or more were included.

Data extraction
The mean difference between baseline and study completion glycated haemoglobin and fasting plasma glucose and its standard error were extracted or estimated for the metformin and sulphonylurea treatment group.

The authors stated neither how the data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
Data for glycated haemoglobin, fasting plasma glucose and risk of hypoglycaemic events were extracted from each study and pooled in meta-analyses. Data on weight change were extracted and tabulated.

The pooled weighted mean differences for glycated haemoglobin and fasting plasma glucose were calculated using a DerSimonian and Laird random-effects meta-analysis.

The pooled odds of symptomatic hypoglycaemia were calculated using random-effects meta-analysis. Heterogeneity was
considered statistically significant at a p value of 0.1. Between-studies differences in baseline glycated haemoglobin and fasting plasma glucose were compared using one-way ANOVA (Analysis of Variance).

**Results of the review**
Six studies with seven treatment arms and 1,364 patients were included. The number of participants ranged from 262 to 1,172. Studies duration ranged from 16 to 52 weeks.

The pooled decrease from baseline in glycated haemoglobin (0.91%, 95% CI 0.71 to 1.11) and fasting plasma glucose (1.80mmol/L, 95% CI 1.08 to 2.51) was significantly greater in the sulphonylurea-treated group. The odds of experiencing a hypoglycaemic event was significantly higher in sulphonylurea-treated patients (OR 5.28, 95% CI 1.71 to 16.33). Data for these outcomes came from all six studies. The mean weight change ranged from +2.5kg to - 0.1kg, dependant on the comparator treatment (five studies).

Statistical heterogeneity was significant for glycated haemoglobin, fasting plasma glucose and the risk of hypoglycaemic event.

**Authors’ conclusions**
In patients with type 2 diabetes that was not controlled by metformin alone, decrease in glycated haemoglobin achieved by the addition of a sulphonylurea was unlikely to exceed 1% even after titration to maximum tolerated doses. Clinically relevant side-effects such as symptomatic hypoglycaemia and weight gain may be experienced.

**CRD commentary**
The review question and inclusion criteria were clear. The search strategy was good as several databases and other sources were searched and efforts to limit publication and language biases were taken. The authors reported methods designed to reduce reviewer bias and error in the assessment of validity, but not in the selection of studies or extraction of data. The assessment of study validity used appropriate criteria. Recommended methods were used to assess statistical heterogeneity and the use of a a random-effects meta-analysis was appropriate. The conclusions of this generally well-conducted review reflected the overall results, although the lack of any description of how authors selected studies and extracted data may limit the validity of the review findings.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

**Funding**
The first author had received payments from Merck and company for data analysis and medical writing and the second author was an employee of Merck and company at the time the paper was written.

**Bibliographic details**

**PubMedID**
18435668

**DOI**
10.1111/j.1463-1326.2008.00884.x

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Blood Glucose /drug effects; Body Weight /drug effects; Diabetes Mellitus, Type 2 /complications /drug therapy; Drug
Therapy, Combination; Hemoglobin A, Glycosylated /drug effects; Humans; Hypoglycemia /etiology; Hypoglycemic Agents /administration & dosage /therapeutic use; Metformin /therapeutic use; Randomized Controlled Trials as Topic; Sulfonylurea Compounds /administration & dosage /therapeutic use; Treatment Outcome; Weight Gain /physiology

**AccessionNumber**
12008105917

**Date bibliographic record published**
03/02/2009

**Date abstract record published**
02/12/2009

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.