Addition of thiazolidinedione or exenatide to oral agents in type 2 diabetes: a meta-analysis
Pinelli NR, Cha R, Brown MB, Jaber LA

CRD summary
This review found that adding thiazolidinediones or exenatide to oral agents in the management of type 2 diabetes had modest beneficial effects on glycaemic control and were relatively safe with regard to the adverse events studied. Given high levels of variation between included trials, some unclear reporting, and possible language and publication bias, these conclusions should be interpreted with caution.

Authors' objectives
To compare the safety and efficacy of adding thiazolidinediones or exenatide to oral agents in the management of type 2 diabetes.

Searching
MEDLINE, CINHAL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews and EMBASE were searched from inception to March 2008. Peer-reviewed full-text English-language publications were included. Reference lists of relevant publications were examined for relevant studies. Abstracts presented at the American Diabetes Association (2006 and 2007) were also searched.

Study selection
Prospective randomised controlled trials (RCTs) that compared thiazolidinediones (rosiglitazone or pioglitazone) or exenatide plus other oral agents with placebo or active comparators were eligible for inclusion. Eligible participants were non-pregnant adults with type 2 diabetes mellitus. Eligible trials had to be at least 24 weeks duration and report glycated haemoglobin (HbA₁c) in a manner that allowed analysis.

The primary outcome measure was mean change in HbA₁c from baseline to study endpoint. Secondary outcomes were: the proportion of participants reaching HbA₁c goals of less than 7%, mean change from baseline in fasting plasma glucose and body weight, and the occurrence of non-severe hypoglycaemia and gastrointestinal adverse events.

The included trials compared either thiazolidinediones or exenatide with placebo or active controls, but not with each other. They evaluated thiazolidinediones or exenatide plus metformin and/or sulphonylurea, other glucose lowering agents, and subcutaneous insulin (glargine and biphasic aspart). The placebo controls used were sulphonylureas or metformin plus placebo. The active controls were sulphonylureas and/or metformin with or without glargine, aspart, muraglitazar or insulin. Repaglinide was also used as an active control. The mean age of participants ranged from 53 to 61 years, 23 to 74% were women, and 0 to 99% were white. Diabetes duration pf participants ranged from 5.4 to 13 years; body mass index ranged from 25 to 34kg/m² in the included studies.

Two reviewers independently screened studies for inclusion and disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed independently by two reviewers in terms of allocation concealment, randomisation, eligibility criteria, intention-to-treat analysis and withdrawals. Disagreements were resolved by consensus.

Data extraction
Data were extracted for the primary outcome (the mean change in HbA₁c) and the following secondary outcomes: proportion of participants reaching HbA₁c goals of less than 7%; mean change from baseline in fasting plasma glucose and body weight; and the occurrence of non-severe hypoglycaemia and gastrointestinal adverse events. Weighted mean differences (WMDs) for continuous variables and odds ratios (ORs) for dichotomous variables were calculated with their respective 95% confidence intervals (CIs).

An independent reviewer checked the accuracy of the extracted data.
Methods of synthesis
Weighted mean differences or odds ratios and 95% confidence intervals were pooled in random-effects meta-analyses (as substantial statistical heterogeneity was present). Heterogeneity was assessed using the I^2 statistic (I^2>50% represented significant heterogeneity).

Subgroup analyses were performed to investigate the effect of comparator interventions and/or background anti-hyperglycaemic therapies.

Sensitivity analyses were performed to investigate the effects of excluding open label studies.

A funnel plot was used to investigate publication bias.

Results of the review
Twenty-two RCTs were included in the review (n=9,325 participants; range 64 to 1159). Five thiazolidinedione-based regimen and two exenatide-based regimen RCTs were open label studies. Allocation concealment and randomisation methods were adequately described in three double blind RCTs and three open label trials. Inclusion/exclusion criteria were adequately described in all trials. Two trials did not report intention-to-treat analysis. Withdrawals were high for each drug (3 to 38% for thiazolidinediones and 15 to 31% for exenatide).

Glycated haemoglobin (HbA_1c) was significantly reduced with thiazolidinedione-based regimens (WMD -0.80%, 95% CI -1.10 to -0.50; 20 study arms; n=6,587 participants) and exenatide-based regimens (WMD -0.60%, 95% CI -1.04 to -0.16; five study arms; n=2,002 participants) compared with control treatments. These were associated with significant heterogeneity (I^2>95%). Funnel plots suggested the presence of publication bias.

Thiazolidinedione-based regimens (OR 2.27, 95% CI 1.22 to 4.24; nine study arms; 3816 participants) and exenatide-based regimens (OR 2.90, 95% CI 1.28 to 6.55; five study arms; n=1,965 participants) were both significantly better at achieving HbA1c targets of less than 7% compared with control treatments. These were associated with significant heterogeneity (I^2>91%).

Thiazolidinedione-based regimens were associated with significantly lower fasting plasma glucose concentrations than control treatments (WMD -29.58mg/dL, 95% CI -39.27 to -19.89), but fasting plasma glucose concentrations were not significantly different between exenatide-based regimens and control treatments.

Body weight was significantly reduced with exenatide-based regimens (WMD -2.74kg, 95% CI -4.85 to -0.64), but was not significantly different between thiazolidinedione-based regimens and control treatments.

There was no significant relationship between thiazolidinedione-based regimens or exenatide-based regimens and control treatments for the risk of non-severe hypoglycaemia. The most commonly reported adverse effects in the exenatide studies were gastrointestinal; there was a significant increase in nausea (OR 9.02, 95% CI 3.66 to 22.23), vomiting (OR 4.56, 95% CI 3.13 to 6.65) and diarrhoea (OR 2.96, 95% CI 2.05 to 4.26) compared with control treatments.

The results of the sensitivity analyses were similar.

The results of subgroup analyses were also reported.

Authors' conclusions
Thiazolidinediones and exenatide had modest beneficial effects on glycaemic control and were relatively safe with regard to the adverse events studied. Thiazolidinediones produced greater improvement in glycaemic control and exenatide was associated with a reduction in body weight.

CRD commentary
The research question was supported by clear inclusion criteria. Only published English language articles were included, so the review may have been prone to language bias and publication bias (as suggested by the asymmetrical funnel plot).
Two reviewers were involved in study selection, data extraction and validity assessment, reducing the risk of reviewer error and bias.

Trial quality was assessed using appropriate criteria. However, the many of the included trials seemed to have had a number of methodological or reporting flaws, so their reliability is unclear. The pooled data were associated with high levels of heterogeneity (where reported), so may not be reliable. The extent of heterogeneity was also not reported for a number of outcomes.

Due to the high levels of heterogeneity, some unclear reporting and possible language and publication bias, the authors’ conclusions should be interpreted with caution.

One author disclosed honoraria from Aventis and Novo-Nordisk (diabetes drug manufacturers).

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

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