A network meta-analysis to compare glycaemic control in patients with type 2 diabetes treated with exenatide once weekly or liraglutide once daily in comparison with insulin glargine, exenatide twice daily or placebo

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CRD summary
This network meta-analysis concluded that exenatide once weekly and liraglutide (1.2mg or 1.8mg) had similar effects in improving the control of blood glucose in people with type 2 diabetes. The quality of the included trials and the applicability of the results to UK practice are uncertain, meaning that the conclusions may not be fully reliable.

Authors' objectives
To determine the probable relative efficacies of various injected therapies for glycaemic control in people with type 2 diabetes.

Searching
The authors searched EMBASE, MEDLINE and The Cochrane Library to May 2011. The search was limited to publications in English. Search terms were available from the authors. Reference lists of retrieved articles and published abstracts of American and European diabetes conferences were screened. Manufacturers (Eli Lilly, Amylin Pharmaceuticals, Novo Nordisk and Sanofi) were approached for unpublished trial data.

Study selection
Randomised controlled trials (RCTs) of people with type 2 diabetes were eligible for inclusion if they compared two or more of liraglutide once daily (1.2mg or 1.8mg); exenatide twice daily (10 micrograms); exenatide once weekly (2mg); insulin glargine; and placebo or no treatment. Trials had to last at least 24 weeks, and report the mean change in glycated haemoglobin from the start.

In the included trials, the mean participant age ranged from 53 to 59 years. Their duration of diabetes was five to 10 years, in most trials. Mean baseline glycated haemoglobin values varied from 7.5% to 8.7%, and body mass index varied from 26.1kg to 35kg per m². Trials lasted from 24 to 52 weeks. Co-interventions were administered to all groups, in most trials.

The authors did not state how many reviewers were involved in study selection.

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

Data extraction
Data were extracted on the changes in glycated haemoglobin from the start, and their associated standard errors. If the standard error was not available, it was calculated from the standard deviation or 95% confidence interval, or imputed from the other trial data.

The data were extracted by one researcher and checked by another.

Methods of synthesis
The data were synthesised by network meta-analysis in a Bayesian multilevel framework. Placebo was used as the reference treatment. The following models were used: random-effects; random-effects adjusted for baseline glycated haemoglobin; and random-effects adjusted for background therapy. Inconsistency in the network was assessed using a 'node-splitting' approach. A number of sensitivity analyses (including some post hoc analyses) were reported.

Results of the review
Nineteen published and three unpublished RCTs were included (11,049 participants).
The estimated mean differences in glycated haemoglobin relative to placebo were -1.15% (95% CrI -1.31 to -1.00) for exenatide once weekly; -1.01% (95% CrI -1.18 to -0.85) for liraglutide 1.2mg; and -1.18% (95% CrI -1.32 to -1.04) for liraglutide 1.8mg. There was no statistically important difference between exenatide once weekly and either dose of liraglutide. The estimated mean difference in glycated haemoglobin between liraglutide 1.2mg and 1.8mg was 0.17% (95% CrI 0.02 to 0.30). There was important inconsistency between the direct and indirect evidence for some comparisons.

The results were consistent when adjusted for background medications and diabetes duration. Other results were reported. Liraglutide 1.8mg had the highest probability of being the most effective treatment (0.67), followed by exenatide once weekly (0.32).

**Authors' conclusions**
The meta-analysis did not identify any meaningful differences in the reduction of glycated haemoglobin between exenatide once weekly and either dose of liraglutide, suggesting that they had similar glycaemic effects.

**CRD commentary**
The review objectives and inclusion criteria were clear. The search covered a range of relevant databases and included both published and unpublished trials. Limiting the search by language meant that some relevant trials could have been missed. The authors did not assess trial quality, so the risk of bias in the included trials was unclear, but they were all RCTs.

It was unclear if the patients in the included trials were representative of those for whom the drugs are considered in UK practice. Limited review methods were reported, so reviewer error and bias cannot be ruled out. The network meta-analysis used standard methods and an appropriate method was used to assess inconsistency.

The authors’ conclusions reflect the results of the network meta-analysis and are broadly in line with those of previous meta-analyses, but they do not reflect the high probability of liraglutide 1.8mg being the most effective treatment, which was not discussed by the authors. The authors investigated some sources of heterogeneity and inconsistency, but some issues, as they acknowledged, were not considered. This, together with the uncertain quality of the included trials, suggests that the conclusions may not be fully reliable.

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**Implications of the review for practice and research**
**Practice:** The authors stated that characteristics other than the ability to reduce glycated haemoglobin might be important when selecting a glucagon-like peptide-1 receptor agonist (exenatide or liraglutide) for patients with type 2 diabetes.

**Research:** The authors did not state any implications for research.

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