Revisiting the efficacy of long-acting insulin analogues on adults with type 1 diabetes using mixed-treatment comparisons

Sanches AC, Correr CJ, Venson R, Pontarolo R

CRD summary
The review concluded that long-acting insulin analogues were similar in terms of efficacy and safety and offered little to no clinical advantage over conventional human insulin in patients with type 1 diabetes. The authors' conclusions should be considered tentative due to limitations in the evidence base and substantial heterogeneity.

Authors' objectives
To compare the efficacy and safety of glargine, detemir and neutral protein Hagedorn (NPH) insulin in adults with type 1 diabetes with respect to incidence of hypoglycaemia, glycated haemoglobin (HbA1c) levels and withdrawals due to adverse events or lack of efficacy.

Searching
Scopus, PubMed, The Cochrane Library, LILACS and IPA were searched from January 1995 to December 2010 without language restriction for relevant studies; search terms were reported. Reference lists of relevant studies and systematic reviews were searched.

Study selection
Randomised controlled trials (RCTs) of adults with established type 1 diabetes were eligible for the review. Studies were required to assess long-acting insulin analogues (glargine or detemir) or NPH insulin either alone or in combination with rapid-acting human insulin or insulin analogues (lispro or aspart) for at least four weeks. The outcomes of interest were change in HbA1c at the end of the study, incidence of overall and nocturnal hypoglycaemic episodes (defined as the number of patients with at least one episode during the study) and withdrawals resulting from a lack of efficacy or adverse events. Studies that used a crossover methodology were excluded.

In the included studies, 47.2% of participants were male and the mean age was 39.3 years. Mean body mass index was 24.9. Mean duration of diabetes was 15.7 years. Seven trials compared glargine with NPH, seven trials compared detemir with NPH and two trials compared glargine with detemir. Dosage of glargine varied from 0.27 to 0.66 units per kilogram per day, dosage of detemir ranged from 0.31 to 0.48 units per kilogram per day and dosage of NPH varied from 0.28 to 0.64 units per kilogram per day (where reported). Trial duration ranged from four weeks to 108 weeks.

Two reviewers independently selected studies for the review.

Assessment of study quality
The studies were assessed for quality using the Jadad scale; criteria were not reported.

The authors did not state how many reviewers assessed studies for quality.

Data extraction
Data were extracted on the outcomes to enable calculation of odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, each with 95% confidence intervals (CIs).

Two reviewers independently extracted data. Discrepancies were resolved through consensus or consultation with a third reviewer.

Methods of synthesis
The results of the studies were pooled in meta-analyses and summary effect odds ratios and mean differences, together with 95% CIs, were calculated using a random-effects model. Heterogeneity was assessed using the $I^2$ index. Where values of $I^2$ were greater than 50%, sensitivity analyses were performed to determine whether study characteristics and statistical methods could have influenced the results. Subgroup analyses were undertaken according to detemir regimen...
(once or twice daily).

A mixed treatment comparison was undertaken using a random-effects model within a Bayesian framework with the Markov chain Monte Carlo method. The outcomes of HbA1c were modelled in every study and relationships among the relative effects across studies were assessed. Different insulin regimens were ranked in terms of efficacy.

**Results of the review**

Sixteen RCTs (glargine 1,508 patients, detemir 2,698 patients, NPH 2,439 patients) were included in the review. Study quality of 15 studies varied from zero to 5 on the Jadad scale; only three studies had scores of 3 or greater.

**Efficacy:** There was no evidence of a statistically significant difference between NPH insulin and detemir once a day in the change of HbA1c at the end of study (MD -0.11%, 95% CI -0.32 to 0.11; I²=71%; two studies). Detemir twice a day was associated with a significant reduction in HbA1c when compared to NPH insulin (MD -0.14%, 95% CI -0.22 to -0.07; I²=0%; five studies) and the overall summary effect favoured detemir (any dose) compared to NPH insulin (MD -0.13%, 95% CI -0.19 to -0.06; I²=13%; seven studies).

There was no evidence of a statistically significant difference between NPH insulin and glargine insulin (MD -0.06%, 95% CI -0.14 to 0.02; I²=44%; seven studies) or between glargine and detemir (MD -0.07%, 95% CI -0.19 to 0.06; I²=0%; two studies).

Network meta-analysis did not find significant differences between treatments. Ranking analysis indicated that NPH insulin was first, detemir second and glargine third.

**Safety and tolerability:** There was no evidence of significant differences between glargine and NPH insulin, between detemir and NPH insulin and between glargine and detemir with regards to frequency of any hypoglycaemic episode or nocturnal hypoglycaemic episode; many of these analyses showed marked heterogeneity. The incidence of withdrawals was not described in the glargine RCTs.

Detemir was associated with a significantly higher incidence of withdrawals than NPH because of adverse events (2.9% versus 0.6%; p<0.001) and a significantly lower incidence of withdrawals because of lack of efficacy (0.4% versus 1.2%; p=0.02). There was no evidence of differences in withdrawal rates when glargine was compared with detemir.

Sensitivity analyses with the removal of individual studies did not markedly change the results.

**Authors' conclusions**

The long-acting insulin analogues offered little to no clinical advantage over NPH insulin and there was no significant difference in efficacy and safety between glargine and detemir.

**CRD commentary**

The review addressed a clear research question supported by appropriate inclusion criteria. Relevant sources were searched to identify studies without language restrictions, which minimised the chance of language and publication biases. Publication bias was not formally assessed. Appropriate methods were used to select studies and extract data but the authors did not state how many reviewers assessed studies for quality. Few studies were high quality and the authors acknowledged that there was difficulty in the masking of insulin regimens, so bias from the included studies could not be ruled out. Reported dosages and schedules of the insulin regimens, laboratory reference values for hypoglycaemic episodes and treatment durations varied. Studies were appropriately combined in meta-analyses. Many of the results showed substantial heterogeneity which limited the robustness of the findings. However, sensitivity analyses that explored the variation did not markedly change the results.

The authors’ conclusions should be considered tentative due to limitations in the evidence base and substantial heterogeneity.

**Implications of the review for practice and research**

**Practice:** The authors stated that choice of insulin regimen could be based on a cost minimisation approach.

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