Comparative effectiveness, safety, and indications of insulin analogues in premixed formulations for adults with type 2 diabetes

CRD summary
This review concluded that premixed insulin analogues provided glycemic control similar to that of premixed human insulin, and may provide tighter glycaemic control than long-acting insulin analogues and non-insulin diabetic agents. This was a generally well-conducted review, however, the conclusions seemed overly strong given the evidence presented, and should be treated with some caution.

Authors' objectives
To determine the effectiveness and safety of premixed insulin analogues in adults with type 2 diabetes.

Searching
MEDLINE, EMBASE, CENTRAL and CINAHL were searched for English language articles. Search dates spanned 1966 to February 2008. The search strategy was reported. Contents pages of 13 relevant journals were searched from June to Sept 2007. Reference lists of included studies were scanned. Information from the Scientific Resource Centre was accessed, including clinical trials registers. Abstracts were excluded.

Study selection
Randomised and non-randomised controlled trials (RCTs and non-RCTs) and controlled observational studies of premix insulin analogues approved by the USFDA compared to another antidiabetic agent in adults with type 2 diabetes were eligible for inclusion. Studies recruiting a mixed population with no separate results for those with type 2 diabetes, were included if at least 75 per cent of participants had type 2 diabetes. Included studies evaluated insulin aspart 70/30, lispro 75/25 or lispro 50/50. Comparators included: each other; premixed human insulin; oral agents; long-, intermediate- or rapid-insulin (or a combination of these); or exenatide. The median age of participants was 59 years (range 51 to 68 years) and the proportion of males was 52 per cent (range 16 per cent to 92 per cent). The mean duration of diabetes was 11 years (range 4 to 16 years). Two independent reviewers selected studies for the review; differences were resolved by discussion.

Assessment of study quality
Study quality was assessed by two independent reviewers in terms of: clarity of the research question; randomisation; similarity at baseline; blinding; ascertainment of exposure and demonstration that the outcome of interest was not present at baseline; methods used to assess primary outcomes; adjustment for key confounders; follow-up; appropriateness of the conclusions; funding source and conflicts of interest, where appropriate to the study design. Studies were rated as good, fair or poor quality. External validity was assessed in terms of the population recruited, excluded and the similarity with the US diabetic population and clinical practice. Differences were resolved by discussion.

Data extraction
Odds ratios (OR) for binary outcomes and mean differences for continuous outcomes, along with 95% confidence intervals (CI), were extracted or calculated from each study. Adverse events were extracted or converted to episodes per patient per 30 days. Data were extracted by one reviewer and checked for accuracy by a second; differences were resolved by discussion.

Methods of synthesis
Pooled OR and weighted mean differences (WMD) and 95% CI were calculated using a random effects meta-analysis. A fixed effect meta-analysis was conducted for rare outcomes, and Peto’s method, Mantel-Haenszel fixed effect meta-analysis and Bayesian methods were used as sensitivity analyses. Heterogeneity was assessed using $X^2$ and $I^2$ tests. Cross-over trials were only included in the assessments of the intermediate outcomes, A1c, fasting glucose and postprandial glucose; analyses were conducted without cross-over trials as sensitivity analyses. Publication bias was assessed visually using a funnel plot and statistically using Begg's, Egger's and the trim-and-fill methods.
Results of the review
Forty five studies across 50 publications were included in the review (n=14,603; range 8 to 8,166); 43 studies were RCTs, of which 23 were parallel group and 20 were cross-over in design. Randomisation was reported in 17 RCTs and considered adequate in 16. Patients were blinded in five RCTs, and outcome assessors in two. Forty studies were stated as recruiting samples representative of the general US diabetic population; only 11 studies were conducted in North America and the remainder were in Europe (16 studies), Asia (six studies), Africa (one study), were multinational (nine studies) or did not state region (two studies). Women were under-represented in five RCTs and men in two RCTs.

In terms of decreasing fasting glucose, premixed insulin analogues were less effective than long-acting insulin analogues (WMD 12.0; 95% CI: 6.0, 18.1; 11 studies) and more effective than non-insulin diabetic agents (WMD -20.5; 95% CI: -29.9, -11.2; 10 studies); there was no significant difference when compared to premixed human insulin (10 studies).

When considering changes in postprandial glucose level, premixed insulin analogues were more effective than long-acting insulin analogues (WMD -27.9; 95% CI: -34.3, -21.5; 9 studies), non-insulin diabetic agents (WMD -37.4; 95% CI: -61.0, -13.7; 10 studies) and premixed human insulin (WMD -19.2; 95% CI: -25.9, -12.5; eight studies). Premixed insulin analogues were more effective in reducing haemoglobin A1c levels than long-acting insulin analogues (WMD -0.39; 95% CI: -0.50, -0.28; 11 studies) and non-insulin diabetic agents (WMD -0.49; 95% CI: -0.86, -0.12; 10 studies), but not premixed human insulin.

Results for comparisons for each type of premixed insulin analogue were reported. The results for a range of secondary outcomes were also reported, including the incidence of hypoglycaemia, mortality and quality of life. There was evidence of publication bias for some of the comparisons where sufficient studies were available for assessment (details provided).

Authors’ conclusions
Premixed insulin analogues provided glycemic control similar to premixed human insulin and may provide tighter glycaemic control than long-acting insulin analogues and non-insulin diabetic agents.

CRD commentary
The review addressed a well-defined research question in terms of participants, interventions and study design. Several relevant sources were searched, but publication and language bias cannot be ruled out; publication bias may have been detected for some outcomes, but was not investigated for all outcomes due to a lack of studies. Each stage of the review was conducted in duplicate, which reduced the risk of error and bias. Study quality was assessed using appropriate criteria. Summary results were provided for each comparison. There seemed to be substantial clinical heterogeneity between studies, so the pooling of results may not have been appropriate; the impact of this did not seem to be investigated. Although this was a generally well-conducted review, the conclusions drawn by the authors seemed overly strong given the evidence presented, and should be treated with some caution.

Implications of the review for practice and research
Practice: the authors did not state implications for practice.
Research: the authors stated that studies were needed that: compared different premixed insulin analogues; compared prandial rapid-acting insulin analogue injections and long-acting insulin analogues; had less restrictive inclusion criteria; investigated subgroups of interest; had longer-term follow-up; and recorded hard clinical outcomes, safety outcomes, quality of life and adherence in addition to intermediate outcomes.

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