Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus

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CRD summary
The authors of this reasonably well-conducted review concluded that inhaled insulin offers an alternative noninvasive option, with comparable glycaemic efficacy and increased patient acceptability, when compared with subcutaneous regular insulin for patients with diabetes. However, they emphasised the need for further research to determine the role of inhaled insulin in diabetes treatment.

Authors' objectives
To investigate the efficacy, safety and patient acceptability of inhaled insulin therapy in adults with diabetes.

Searching
MEDLINE(1966 to June 2006) and the Cochrane Controlled Trials Register(from Issue 2, 2006) were searched; the search terms were reported. The authors also searched for additional publications in reference lists. Unpublished studies were sought through a briefing document on Exubera. Only articles reported in the English language were eligible.

Study selection
Study designs of evaluations included in the review
To be eligible, the studies needed to be randomised controlled trials (RCTs). Letters, abstracts and conference proceedings not published in peer-reviewed journals were excluded. All except one study were parallel trials.

Specific interventions included in the review
To be eligible, the trials needed to compare inhaled insulin with another active therapy (subcutaneous insulin or oral hypoglycaemic agents) over a period of 12 weeks or greater. Most of the trials were of 24 weeks' duration or less. The inhaled insulin device used in the majority of the trials was Exubera, produced by Pfizer Inc.

Participants included in the review
To be eligible, the participants needed to be non-pregnant adults with type 1 or type 2 diabetes mellitus. All trials selected patients without a recent history of smoking (at least 6 months) or underlying pulmonary disease. The participants were aged from 18 to 80 years. Eighty-six per cent of the participants were white.

Outcomes assessed in the review
To be eligible, the trials needed to report haemoglobin (Hb) A1c levels. The primary outcome was the treatment group difference in the change in HbA1c level from baseline. The secondary outcome was the proportion of participants achieving HbA1c levels of less than 7%. Safety outcomes were severe hypoglycaemia, cough and treatment group differences in changes in pulmonary function variables. Patient acceptability and change in body weight were also investigated.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed trials for inclusion, with any differences resolved by consensus.

Assessment of study quality
The following were used to assess study quality: allocation generation, intention-to-treat analysis, drop-out rate, and whether the trial was designed to test glycaemic efficacy noninferiority or superiority. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted data, with any differences resolved by consensus. The safety data extracted related to severe hypoglycaemia, pulmonary symptoms, change in pulmonary function and level of circulating insulin antibodies. Data were gathered on the total number of patients per treatment group who reported at least one episode of severe hypoglycaemia. The Food and Drug Administration's definition of hypoglycaemia was used (patient had a blood glucose level less than or equal to 2 mmol/L (i.e. 36 mg/dL) or required assistance).

For continuous variables, the weighted mean difference (WMD) and its associated 95% confidence interval (CI) were calculated, based on the change from baseline in the inhaled insulin group versus the comparison group. For dichotomous variables, the risk ratio (RR) and its associated CI were calculated. Publicly available information was used to supplement published reports.

**Methods of synthesis**

*How were the studies combined?*

The studies were grouped according to the type of control (subcutaneous insulin or oral hypoglycaemic agents) and combined in meta-analyses. There were insufficient data to perform meta-analyses on nonglycaemic outcomes. Weight change as an outcome could only be assessed using meta-analysis for inhaled insulin versus oral hypoglycaemic agents. For all meta-analyses the authors used a random-effects model weighted by the inverse of the within-study and between-study variances. Intention-to-treat analyses were used when available.

*How were differences between studies investigated?*

The I-squared statistic was used to assess the level of heterogeneity among trials in each meta-analysis. Subgroup analyses were also conducted according to type of diabetes and length of trial.

**Results of the review**

Sixteen open-label RCTs (4,023 patients) were included.

No trials reported attempts to blind the outcome assessors, and none used a double dummy technique to blind patient and physician. All trials comparing inhaled insulin with subcutaneous insulin were designed to test 'noninferiority', whereas those comparing inhaled insulin with oral agents were designed to show 'superiority' of inhaled insulin. Seven of 12 trials used intention-to-treat analysis.

**Glycaemic outcomes.**

**Inhaled insulin versus subcutaneous insulin.**

Based on 11 studies in patients with type 1 or type 2 diabetes, there was a statistically significant difference in the decrease in haemoglobin levels from baseline favouring subcutaneous insulin (WMD 0.08%, 95% CI: 0.03, 0.14). Two studies of 104 weeks' duration gave a WMD of 0.18% (95% CI: 0.09, 0.27), but studies of less than 24 weeks' duration demonstrated no difference between treatments. Trials of patients with type 1 diabetes had a WMD of 0.09% (95% CI: 0.03, 0.16), whereas those of patients with type 2 diabetes showed no statistically significant difference between treatments. There was no heterogeneity between trials. Based on 5 trials, there was no difference between the proportion of patients who achieved HbA1c levels of less than 7%.

**Inhaled insulin versus oral hypoglycaemic agents.**

Based on 6 trials in patients with type 2 diabetes, inhaled insulin lowered HbA1c levels more than oral agents (WMD -1.04%, 95% CI: -1.59, -0.49); there was some heterogeneity between trials. The larger 2 trials, which had a duration of 24 weeks and titrated the dose of therapy in both groups to achieve glycaemic targets, had a smaller, although still statistically significant, mean difference than the other trials. Patients taking inhaled insulin were more likely than those taking oral agents to achieve HbA1c levels of less than 7% (RR 1.87%, 95% CI: 1.07, 3.25).

**Safety.**

Severe hypoglycaemia was more likely in patients taking inhaled insulin than in those taking oral agents (RR 3.06, 95%
CI: 1.03, 9.07). There was no difference between inhaled insulin and subcutaneous insulin. There was an increased incidence of mild to moderate nonprogressive dry cough in patients taking inhaled insulin compared with oral agents or subcutaneous insulin (RR 3.52, 95% CI: 2.23, 5.56). Two per cent of patients with type 1 diabetes and 2.3% with type 2 diabetes discontinued inhaled insulin treatment due to respiratory events compared with 0% and 0.1%, respectively, taking either subcutaneous insulin or oral agents.

Patient-reported outcomes.

Based on 4 trials of patients with either type 1 or type 2 diabetes, there was a statistically significant increase in overall patient satisfaction with inhaled insulin over subcutaneous insulin. Two studies reported statistically significant improvements in overall quality of life with inhaled insulin, and in 2 further studies patients randomly assigned to inhaled insulin were more likely to continue with it than to switch back to subcutaneous insulin.

Authors' conclusions
Inhaled insulin offered an alternative, noninvasive option with slightly less glycaemic efficacy to subcutaneous regular insulin and increased patient acceptability. However, the authors emphasised the need for further research to determine the role of inhaled insulin in diabetes treatment.

CRD commentary
The review addressed a clear question with defined inclusion criteria for the participants, interventions, outcomes and study designs. The search was appropriate, but some unpublished studies might have been missed and the review was limited to English language articles only. Two reviewers were involved in the selection of studies and data extraction, thus helping to minimise bias. The validity of the included studies was assessed and discussed in the context of the results.

The meta-analysis appeared to have been conducted appropriately, with results also being presented for subgroup analysis based on diabetes type and length of study. It should be noted that the studies comparing inhaled insulin with subcutaneous insulin were designed as equivalence trials, not as superiority trials, and so might have underestimated the effects of inhaled insulin. The review appeared to be a reliable synthesis of the trials in this area and appropriately pointed to the need for further research on inhaled insulin.

Implications of the review for practice and research
Practice: The authors concluded that until long-term safety data become available, inhaled insulin should be reserved for non-pregnant adults without pulmonary conditions who are opposed to injections and who would otherwise delay taking their insulin.

Research: The authors stated that studies of longer duration are needed to assess the effects of inhaled insulin on lung function.

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