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Volume 58 Issue 4

DRUG FOCUS

Exubera inhaled insulin: a review

A.H. Barnett^{1*}

Summary

The focus of this review is inhaled insulin, specifically Exubera™, which represents a novel prandial insulin delivery method. Fear of hypoglycaemia and the reluctance of patients to use multiple daily injection regimens is a major barrier to achieving good glycaemic control in patients with type 1 and type 2 diabetes. Inhaled insulin has been developed to provide more physiological prandial insulin replacement than regular human insulin in patients with diabetes, with the advantage of non-invasive delivery. Good glycaemic control, comparable to modern subcutaneously administered insulin preparations, has already been demonstrated, and no unexpected safety concerns have been reported with inhaled insulin. The development of such insulin delivery technologies that are better tailored to patients' needs may improve patient compliance, thereby facilitating the attainment of treatment targets. This review summarises the studies available and discusses the potential implications to patients of needle-free insulin administration.

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Introduction

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Despite continuing therapeutic advances, the incidence of both type 1 and type 2 diabetes is continuing to increase, the latter at epidemic proportions. Tight glycaemic control remains the primary target for modern intensive treatment strategies for both forms of diabetes, in order to prevent the development of long-term complications, and therefore reduce morbidity and mortality (1,2). Multiple daily injections of basal and bolus insulins are the mainstay of insulin delivery for the majority of patients with type 1 diabetes. Despite the more favourable time–action profiles of modern insulin analogues (which are optimising glycaemic control), many patients are still suboptimally controlled (3) and dislike multiple injection regimens (4); alternative insulin delivery methods could provide a significant advantage in terms of patient acceptability and adherence.

A number of delivery systems are therefore being developed to overcome patient acceptability problems with injected insulin formulations. These include pulmonary insulin delivery, which is a potentially convenient and effective diabetes therapy. Exubera (inhaled insulin) is a non-invasive dry powder insulin inhalation system that is designed to deliver human insulin to the lung alveoli and is being investigated in Phase III trials by Aventis and Pfizer. This review discusses the profile of Exubera and its potential clinical implications on diabetes care.

How exubera works

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The concept of inhaled insulin was first investigated in Germany in 1925, where the use of a nebuliser to deliver insulin was investigated (5). Then, in 1971, Wigley and colleagues (6) administered aerosolised insulin, via a nebuliser, to rabbits and showed a hypoglycaemic effect. Delivery technology has since advanced and it is accepted that for inhaled insulin to be effective, the particle size must be small enough to enter the lungs (1–3 µm), but large enough not to be exhaled (7).

Exubera works because of the large surface area and high permeability of the lungs, which mean that insulin can be effectively absorbed into the systemic circulation via the alveoli, with minimal absorption in the bronchi. Transcytosis is the primary mechanism of insulin absorption across the alveolar capillary and epithelial cells (Figure 1) (8). Exubera comprises spray-dried human recombinant insulin (particle diameter 1–5 µm), which is packaged into blisters in combination with an inhaler device (Figure 2). Each blister contains either 1 or 3 mg of insulin made up to a total weight of 5 mg with mannitol, glycine and sodium citrate. A single administration of these doses delivers the equivalent of approximately 3 IU or 9 IU of subcutaneous (sc) insulin, respectively.

Exubera clinical pharmacology

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Regular human insulin (RHI) is often used to fulfil prandial insulin requirements in patients with diabetes, but does not adequately mimic physiological insulin secretion patterns (9). Inhaled insulin has been developed to have a more rapid onset of action compared with sc RHI. A number of pharmacokinetic and pharmacodynamic studies have compared inhaled insulin with sc RHI and with sc rapid-acting insulin analogues, and evaluated its time–action profile.

In general, the time–concentration profile of inhaled insulin is similar to that of physiological insulin secretion in response to meals. This has been demonstrated in a non-diabetic volunteer study ($n = 11$) comparing the pharmacodynamics of inhaled microcrystalline solid insulin (99 IU) with sc injections of RHI (10 IU) and intravenous injections of RHI (5 IU), using a euglycaemic clamp technique (10). Onset of action was significantly faster for inhaled insulin compared with sc RHI (31 vs. 54 min; $p < 0.001$), as was time to maximal metabolic response (108 vs. 147 min; $p < 0.001$). Inhaled insulin was associated with a rapid increase in serum insulin concentrations to maximum values compared with sc insulin (82 min earlier after inhaled insulin) (Figure 3).

Another euglycaemic clamp study conducted in non-diabetic volunteers ($n = 18$) showed that inhaled insulin (6 mg) had a faster onset of action

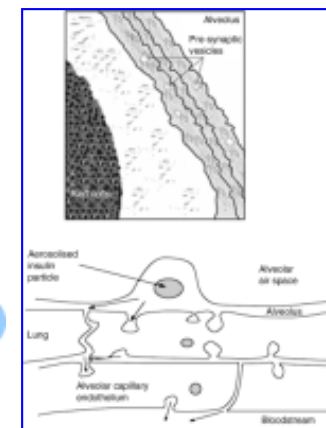
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Figure 1 Transcytosis of inhaled insulin. Exubera molecules become trapped in the alveoli and are take...

compared with RHI (18 IU) and insulin lispro [half life (t) 32, 48 and 40 min, respectively] (11). Maximal metabolic activity was similar for all the three groups and the duration of action for inhaled insulin (382 min) fell between those of insulin lispro and RHI (309 and 413 min, respectively).

Similar studies have been conducted in patients with type 2 diabetes: one study showed peak insulin levels 43 min post-administration for inhaled insulin compared with 64 min for sc RHI; bioavailability was 15% for inhaled insulin vs. sc RHI (12). Another study showed that inhaled insulin administered as 4–6 inhalations of a 20% dry powder formulation provided similar reductions in post-prandial hyperglycaemia and comparable reproducibility vs. 0.2 IU/kg sc RHI (13).

These studies suggest that the time–action profile of inhaled insulin is better suited to prandial glucose control compared with RHI.

Efficacy of exubera

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Phase II Studies

A number of Phase II proof-of-concept studies have been conducted with inhaled insulin in patients with type 1 and type 2 diabetes. Inhaled insulin demonstrated significant reductions in HbA_{1c} and comparable overall glycaemic control with sc insulin in patients with type 1 diabetes. These effects have been reproduced in patients with type 2 diabetes and in special patient populations. These studies are discussed in more detail below.

Patients with type 1 diabetes.

A US-based, 12-week, randomised study in which 73 insulin-pre-treated (2–3 injections per day) patients with type 1 diabetes received either inhaled insulin plus sc ultralente or their former sc insulin regimen (RHI/NPH insulin) showed similar HbA_{1c} reductions from baseline (mean baseline HbA_{1c} 8.5%) in both groups [endpoint 7.9 vs. 7.7%; between-treatment difference 0.2 and 95%; confidence interval (CI): –0.2, 0.5] (Figure 4) (14).

Furthermore, there were no between-treatment differences in fasting and post-prandial blood glucose level baseline-to-endpoint changes or in the occurrence or severity of hypoglycaemia. These results are supported by another Phase II study involving 70 patients with type 1 diabetes, which showed that reductions in HbA_{1c} and hypoglycaemia incidence and severity were similar for inhaled or sc insulin-treated patients (15).

Patients with type 2 diabetes.

Similar studies have been conducted in patients with type 2 diabetes who had previously been treated with insulin; a 3-month, randomised, open-label study in patients with type 2 diabetes ($n = 26$) showed that inhaled insulin produced significant baseline to endpoint improvements in glycaemic control (from 8.67% at baseline to 7.96% at endpoint) in combination with sc ultralente (3). This study was supported by another randomised 3-month study ($n = 51$), in which similar baseline-to-endpoint changes in HbA_{1c} were achieved for inhaled insulin and sc insulin (–0.72 vs. –0.71%) in patients previously treated with insulin; both treatments were safe and well tolerated (16).

A 12-week study investigated the effect of adding inhaled insulin (administered thrice a day before meals) to oral hypoglycaemic agents in 69 insulin-naïve patients with poorly controlled disease (17). The results demonstrated a baseline to endpoint reduction in HbA_{1c} >2% in the combination group compared with no change in the group receiving oral agents only (Figure 5). Within-patient variability has also been assessed in both elderly and obese patients [mean age 72 years; mean body mass index (BMI) 33 kg/m²] with type 2 diabetes (18). The results showed comparable within-subject variability and systemic insulin exposure over 6 h and a faster absorption of inhaled insulin compared with sc insulin.

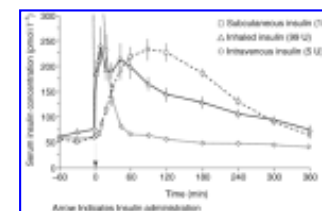
Phase III Studies

Several Phase III studies have supported the efficacy of inhaled insulin in patients with type 1 or type 2 diabetes with reductions in fasting and post-



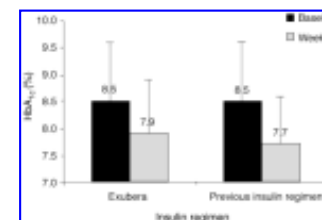
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Figure 2 The Exubera inhaled insulin delivery system



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Figure 3 Serum insulin concentrations after administration of inhaled insulin, subcutaneous insulin an...



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Figure 4 Baseline to endpoint changes in HbA_{1c} over 12 weeks with Exubera and subcutaneous insulin

prandial blood glucose control (Table 1). Furthermore, more patients with type 2 diabetes achieve treatment targets with inhaled insulin regimens than with sc insulin.

Patients with type 1 diabetes.

A 6-month, randomised, multicentre study comparing inhaled insulin with sc RHI, both in combination with morning and evening NPH insulin, in patients with type 1 diabetes demonstrated similar baseline-to-endpoint reductions in HbA_{1c} in both groups. Fasting plasma glucose levels fell in the inhaled insulin group compared with an increase in the sc insulin group (−1.9 vs. 0.2 mmol/l; CI: −3.2, −1.2). Similarly, a decrease in 2-h post-prandial glucose levels was achieved (−1.2 mmol/l for inhaled insulin and −0.78 mmol/l for sc insulin) (19). In another 6-month, randomised, multicentre study involving 335 patients with type 1 diabetes receiving inhaled insulin and sc ultralente or 2–3 injections of sc insulin (NPH/RHI), similar reductions in HbA_{1c} were noted for inhaled and sc insulin, and fasting plasma glucose levels were significantly lower in the inhaled insulin group (−1.94 vs. −0.56 mmol/l; CI: −2.41 vs. −0.39) (Figure 6) (20). In addition, there was also a significant reduction in 2-h post-prandial blood glucose levels for the inhaled insulin group (−1.67 vs. 0.06 mmol/l).

Patients with type 2 diabetes.

A multicentre study conducted in 309 patients with type 2 diabetes failing (HbA_{1c} = 8%) oral agent therapy (a sulphonylurea or repaglinide, plus metformin or a glitazone) showed that inhaled insulin significantly improved HbA_{1c} when used as either monotherapy (−1.4%; p < 0.0001) or in combination with oral agents (−1.9%; p < 0.0001) compared with continuing oral agents alone (−0.2%) over 3 months (Figure 7) (21). A greater proportion of patients achieved HbA_{1c} targets <7 and <8% in both of the inhaled insulin groups compared with oral agents alone (56 and 17%, respectively, for inhaled insulin; 86 and 32%, respectively, for inhaled insulin plus oral agents; 19 and 1%, respectively, for oral agents). Furthermore, there were greater reductions in 2-h post-prandial glucose levels in the inhaled insulin groups compared with oral therapy alone (−2.4 mmol/l for inhaled insulin; −1.3 mmol/l for inhaled insulin and oral agents; −0.1 mmol/l for oral agents).

Inhaled insulin was compared with rosiglitazone in a 3-month, randomised, multicentre Phase III study involving 145 patients with type 2 diabetes, who were not optimally controlled on diet and exercise alone (22). Patients received either inhaled insulin before meals or rosiglitazone (twice daily), in combination with a diet and exercise regimen. More patients achieved HbA_{1c}<8% at endpoint in the inhaled insulin group compared with rosiglitazone (83 vs. 58%; adjusted odds ratio: 7.14; 95% CI: 2.48, 20.58). Furthermore, a greater proportion of patients achieved HbA_{1c}<7% in the inhaled insulin group (44 vs. 18%; adjusted odds ratio: 4.43; 95% CI: 1.94, 10.12), and baseline to endpoint reduction in HbA_{1c} was greater compared with rosiglitazone (−2.3 vs. −1.4%; adjusted difference: −0.98%; CI: −1.23, −0.55) (Figure 8).

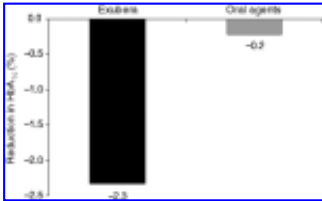
Patients with suboptimally controlled type 2 diabetes (n = 299) receiving either inhaled insulin before meals plus ultralente or two injections of sc insulin (NPH/RHI) showed similar reductions in HbA_{1c} in both the inhaled and sc insulin groups (−0.7 vs. −0.6%) in another Phase III study (23). Similar proportions of patients in both groups achieved HbA_{1c}<8%; however, a significantly greater proportion of inhaled insulin patients achieved HbA_{1c} levels <7% compared with the sc insulin group (46.9 vs. 31.7%; CI: 1.24, 4.14).

Insulin doses

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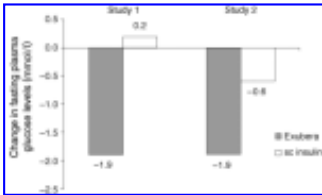
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Limited data on inhaled insulin doses are available although doses are expected to be higher, compared with sc insulin because of limited bioavailability. Two published 12-week, randomised, open-label studies report mean daily prandial insulin dose data in patients with type 1 and type 2 diabetes for inhaled insulin of 12.2 mg (equivalent to 36.6 IU sc insulin) and 14.6 mg (equivalent to 43.8 IU sc insulin), respectively; sc insulin doses were 15.9 and 19.0 IU, respectively (3,14). Further studies are required to make better treatment comparisons.



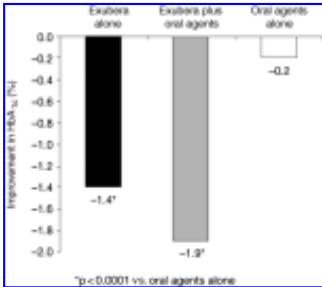
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Figure 5 Better glycaemic control with Exubera vs. oral agents in patients with type 2 diabetes



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Figure 6 Changes in fasting plasma glucose levels in two, 6-month Phase III studies of Exubera and sub...



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Figure 7 Efficacy of Exubera over 3 months in patients with type 2 diabetes

Body weight

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Weight gain is often a concern with insulin therapy, especially in patients with type 2 diabetes. In studies where body weight data have been reported, overall, inhaled insulin shows a slight increase in body weight (range −0.3 to 2.8 kg) comparable with that seen with sc insulin (range +0.7 to 0.9 kg) or oral agents (+0.8 kg) (3,14,20,21,24).

Hypoglycaemia

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Inhaled insulin is associated with similar hypoglycaemia rates to sc insulin, and no increase in the incidence or severity of hypoglycaemic episodes has been noted in patients with either type 1 or type 2 diabetes. Only one 3-month, Phase III study reported a slightly higher rate of hypoglycaemic episodes in patients with type 2 diabetes (1.7 events/patient–month for inhaled insulin plus orals agents; 1.3 events/patient–month for inhaled insulin; 0.1 events/patient–month for oral agents) (21), compared with the other studies discussed in this review, which have shown no increase in hypoglycaemia with inhaled insulin.

Effects on pulmonary function

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This is an important consideration for inhaled insulin therapy. The American Conference of Governmental Industrial Hygienists has determined that the lungs have a threshold limit value for inhalation of insoluble ‘nuisance dust’ of 30 mg/day (25). Inhaled insulin is rapidly absorbed from the epithelial surface of the lungs and therefore will only deposit up to an average of 10 mg (range 1–20 mg) per work day of insulin in the lungs (7). This means that therapeutic daily doses of inhaled insulin should not adversely affect lung function. In general, pulmonary function has been stable in patients with type 1 and type 2 diabetes, who have been treated with inhaled insulin, and no clinically significant differences in the main measures of pulmonary function (spirometry, lung volume, diffusion capacity or oxygen saturation) have been noted compared with patients on sc insulin therapy (3,13,14,16,19–21,23,24,26). Most of the studies discussed earlier in this article report only limited pulmonary function data; the main findings are summarised in Table 2.

Only one, 12-week, open-label, proof-of-concept, parallel-group, randomised study involving patients with type 1 diabetes (*n* = 73) has reported pulmonary function test data in full. Inhaled insulin again showed a similar profile to sc insulin, and mean change from baseline to endpoint in forced expiratory volume in one second (FEV₁) was −2.17 L for inhaled insulin compared with −1.02 L for sc insulin. Mean change in peak expiratory flow rate was 2.41 and 1.21 L/s for respective groups. Mean baseline-to-endpoint changes in total lung capacity were also similar (1.35 L for inhaled insulin and 1.10 L for sc insulin), as were mean changes in diffusion capacity (−5.78 vs. −7.71 ml/min/mmHg, respectively) and oxygen saturation (−0.3 vs. 0.04%, respectively) (14).

Data are limited, however, in patients with chronic obstructive pulmonary disease, emphysema and chronic smokers. Only a few studies have shown differences between inhaled and sc insulin in terms of carbon monoxide diffusing capacity (Table 2). More studies, particularly in special patient populations, will be required to draw firm conclusions although data from existing studies look favourable.

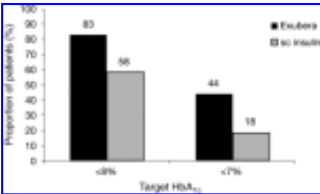
Smoking

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Smoking is as common in patients with diabetes as in the general population (27). Because smoking has been shown to increase the permeability of the alveolar–capillary barrier in animal and human studies (28,29), inhaled insulin dose requirements may be lower in smokers. Subcutaneous insulin absorption, however, is decreased in smokers (30) and insulin action may be impaired leading to insulin resistance (31) necessitating larger sc insulin doses.



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Figure 8 The proportion of patients with type 2 diabetes meeting treatment targets

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Table 1 Summary of data from Exubera Phase III studies

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Table 2 Summary of pulmonary function test data from Exubera studies

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The effect of smoking cessation on the absorption of inhaled insulin has been compared in volunteer smokers ($n = 38$) and non-smokers ($n = 30$) (32). At baseline, peak insulin concentrations ($C_{\max}$) and total insulin exposure were fivefold and threefold higher in smokers compared with non-smokers, and $C_{\max}$ occurred earlier in smokers than in non-smokers (31 vs. 53 min). Three weeks after smoking cessation, $C_{\max}$ and total insulin exposure had decreased to 49 and 59% of the active smoking levels, respectively. Furthermore, after 13 weeks, changes in inhaled insulin absorption in smokers were partly, but not completely, reversed by smoking cessation. This is an area of particular interest, and patients who smoke should be encouraged to quit before considering inhaled insulin therapy.

Safety of exubera

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The safety of injected insulins has been consistently demonstrated in clinical trials; however, there are fewer data to support the safety of inhaled insulins. In general, safety has been comparable with sc insulin in all studies, with a similar incidence of hypoglycaemia. The safety of intrapulmonary insulin has been demonstrated on rats and cynomolgus monkeys; daily inhalation was well tolerated and no airway or pulmonary lesions were evident (33).

An increase in the incidence of mild-to-moderate cough has been noted in two inhaled insulin studies (approximately 25% of inhaled-insulin patients vs. approximately 5% of sc insulin-treated patients), which is not unexpected with inhalation devices; otherwise, the incidence of adverse events with inhaled insulin has been similar to that seen with sc insulin (19,20).

Increased antibody formation has been reported with insulin analogues in general although the clinical impact (if any) of such increases has yet to be elucidated. Pooled antibody data from Phase II and III (3 and 6-month) studies of inhaled insulin in patients with type 1 and type 2 diabetes have shown that switching from sc insulin to inhaled insulin is associated with an increase in antibody levels, but that these antibodies are not associated with increased HbA_{1c}, insulin doses, hypoglycaemia or allergic reactions (26).

Patient acceptability

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Inhaled insulins are associated with improvements in treatment satisfaction. Such benefits are particularly important in patients with type 2 diabetes who are often reluctant to accept injection-based therapy. This could potentially improve patient compliance and glycaemic control in previously poorly controlled patients.

A 1-year extension study of randomised, 3-month inhaled insulin efficacy studies in patients with type 1 diabetes ($n = 66$) and type 2 diabetes ($n = 47$) demonstrated that inhaled insulin was preferred over sc insulin and that patient satisfaction was better in the short- and long-term (34). Baseline (original study) to endpoint (extension study) improvements in global patient satisfaction scores were significantly better for inhaled insulin compared with sc insulin in terms of treatment satisfaction (39 vs. 4%; $p < 0.01$) and convenience/ease of use (42 vs. -2%; $p < 0.01$). Scores were higher for inhaled insulin in all studies that have reported patient satisfaction data, and statistically significant improvements in global satisfaction, ease of use, patient convenience and social stigma were seen; moreover, patients who switched from inhaled insulin to sc insulin showed a trend towards worsening satisfaction scores (3,15,16,20,23,35). Therefore, the particular benefit of inhaled insulin may lie in this area.

Cost effectiveness

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Greater dosages of inhaled insulin are required to produce similar efficacy to injectable insulin formulations because of the reduced bioavailability by this route.

This means that costs are likely to be higher for inhaled insulins. Such additional costs are likely to be alleviated, however, because of the benefits in

terms of treatment satisfaction and the potential positive impact on treatment adherence and therefore glycaemic control.

Discussion and conclusions

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The benefits of intensive insulin therapy have been clearly demonstrated in studies such as the UK Prospective Diabetes Study (UKPDS) (2) and the Diabetes Control and Complications Trial (DCCT) (1). Despite such obvious advantages, intensive insulin therapy is not widely accepted in routine clinical practice because of the barriers to insulin use, such as hypoglycaemia and the fear and reluctance to use multiple daily injections. Inhaled insulin is a non-invasive method of insulin delivery and therefore should alleviate some of the problems and fears associated with insulin injections.

The studies discussed in this review show that inhaled insulin may have a more physiological insulin profile compared with sc RHI, and that inhaled insulin is a suitable therapy to aid achievement of good glycaemic control and therefore help to prevent the complications of diabetes. Exubera inhaled insulin has demonstrated efficacy in terms of achieving significant reductions in HbA_{1c} and facilitating treatment to recommended HbA_{1c} targets in type 1 and type 2 diabetes. Furthermore, there may be some benefit in terms of further reducing fasting blood glucose levels compared with sc insulin.

The obvious advantage for this therapy lies in patient satisfaction and thus, potentially, adherence to therapy. The impact of inhaled insulin on treatment adherence remains to be fully elucidated; however, it would be reasonable to speculate that in clinical practice more patients will achieve target HbA_{1c} levels and that patients who were previously poorly controlled may improve because of better, patient-tailored therapy.

In conclusion, inhaled insulins such as Exubera represent a promising and novel diabetes therapy and may be of particular benefit in patients who are unreceptive to multiple daily insulin injections.

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Figure 1 Transcytosis of inhaled insulin. Exubera molecules become trapped in the alveoli and are taken up in vesicles by the alveolar epithelial cells. These insulin-containing vesicles are then released between the epithelial cells and the alveolar capillary endothelial cells. Insulin molecules are then taken up within vesicles by endothelial cells, transported across them and then released into the alveolar capillary bloodstream. Adapted from references (7) (8). Permission requested

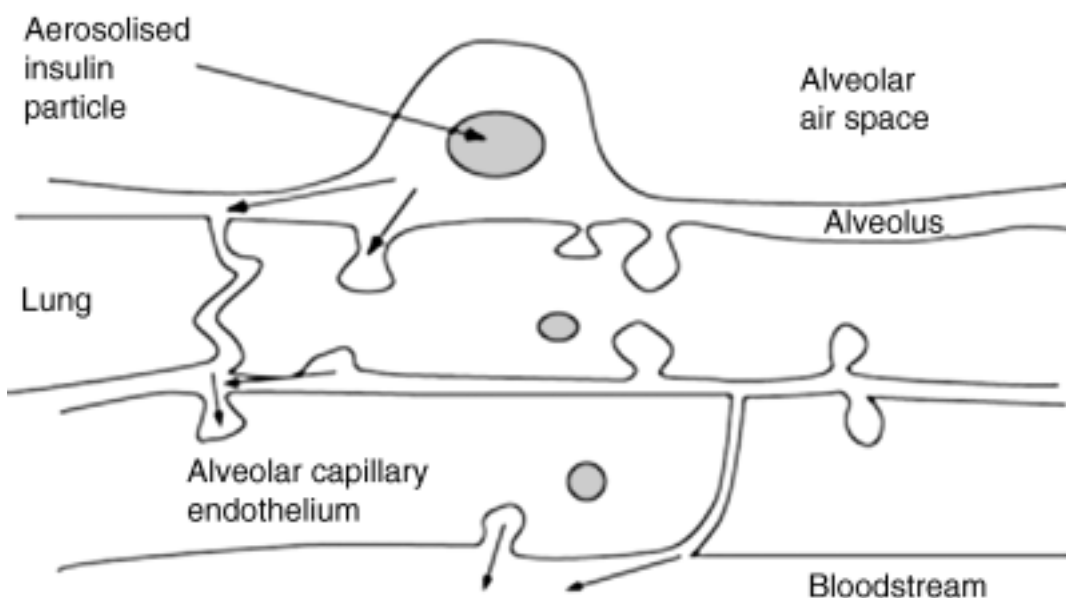
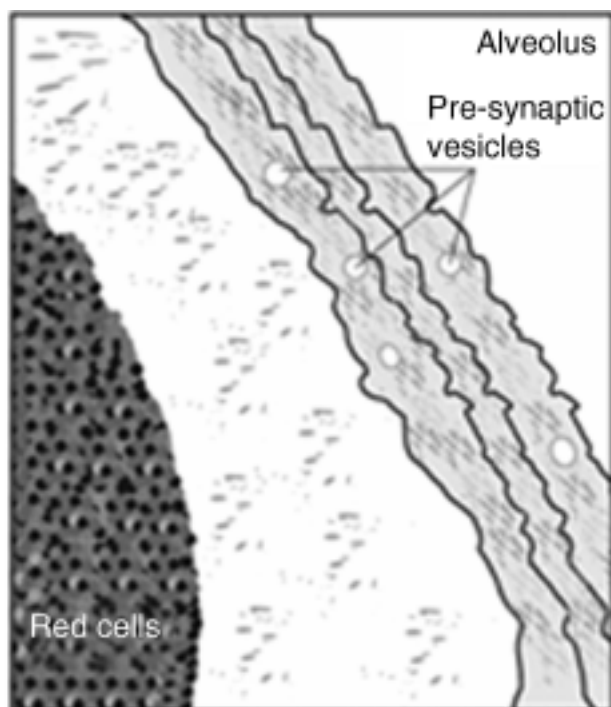


Figure 2 The Exubera inhaled insulin delivery system



Figure 3 Serum insulin concentrations after administration of inhaled insulin, subcutaneous insulin and intravenous insulin in healthy volunteers. Reproduced from reference (10) with permission of Blackwell Science. © Blackwell Science

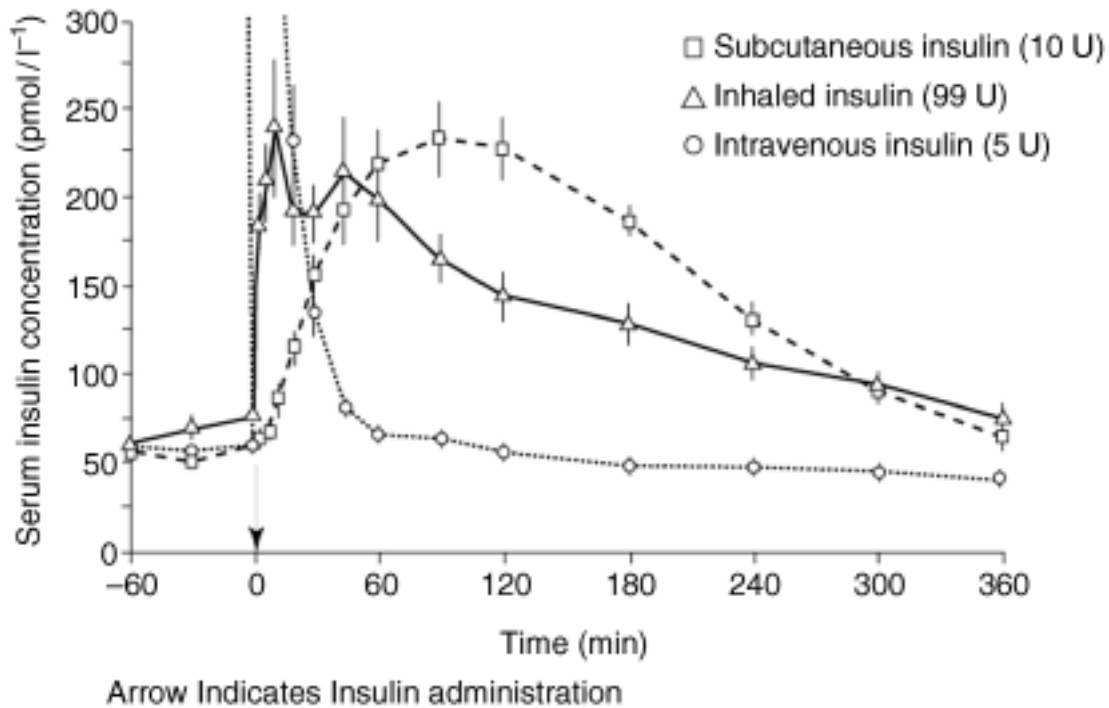


Figure 4 Baseline to endpoint changes in HbA_{1c} over 12 weeks with Exubera and subcutaneous insulin

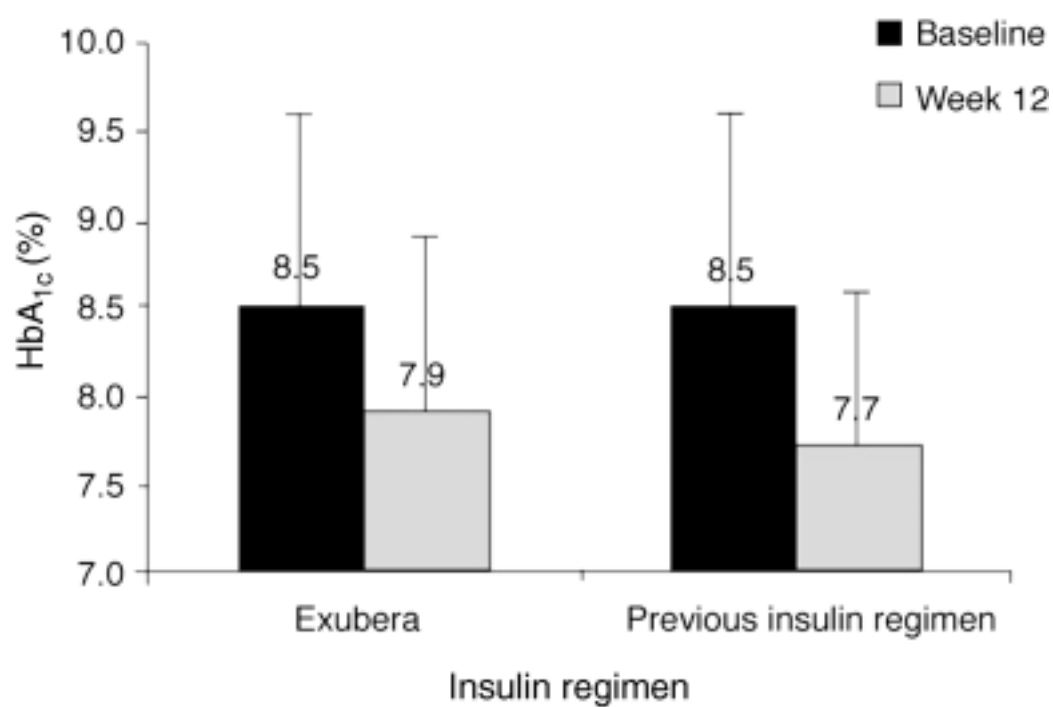


Figure 5 Better glycaemic control with Exubera vs. oral agents in patients with type 2 diabetes

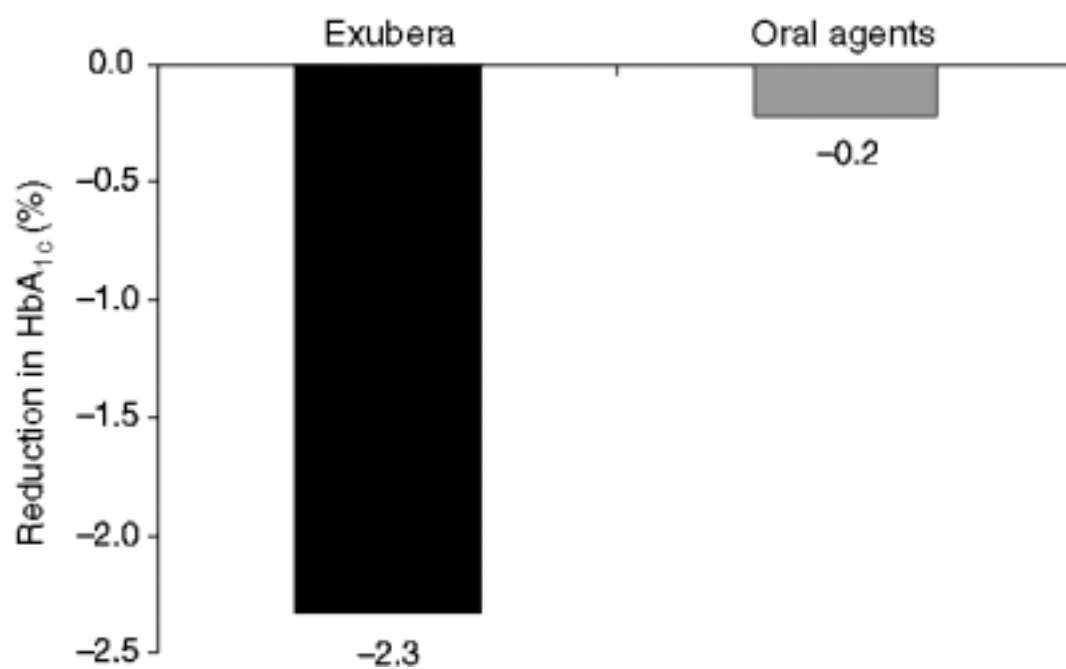


Figure 6 Changes in fasting plasma glucose levels in two, 6-month Phase III studies of Exubera and subcutaneous insulin in patients with type 1 diabetes. [Study 1 ([19](#)); Study 2 ([20](#))]

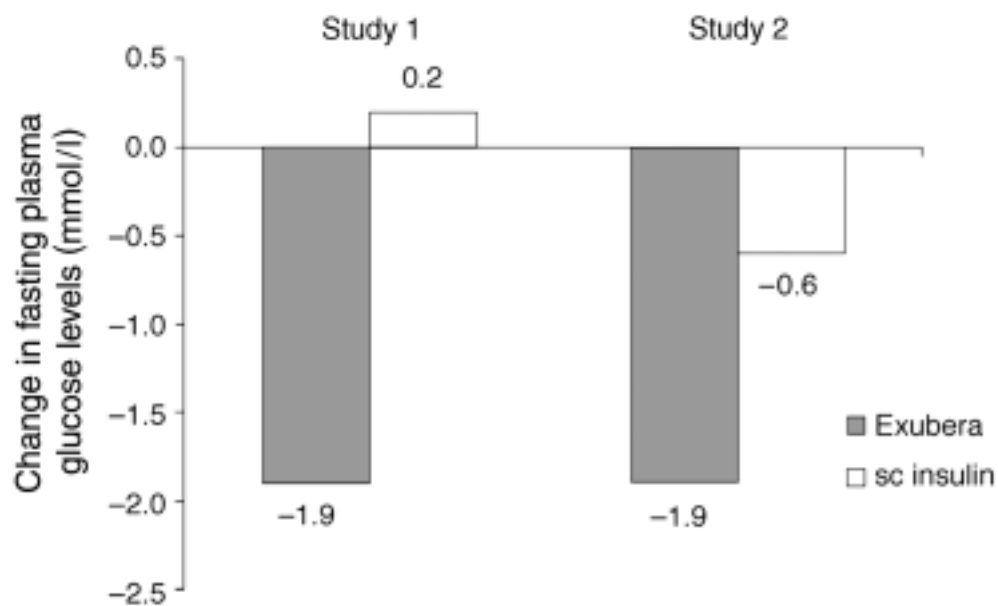


Figure 7 Efficacy of Exubera over 3 months in patients with type 2 diabetes

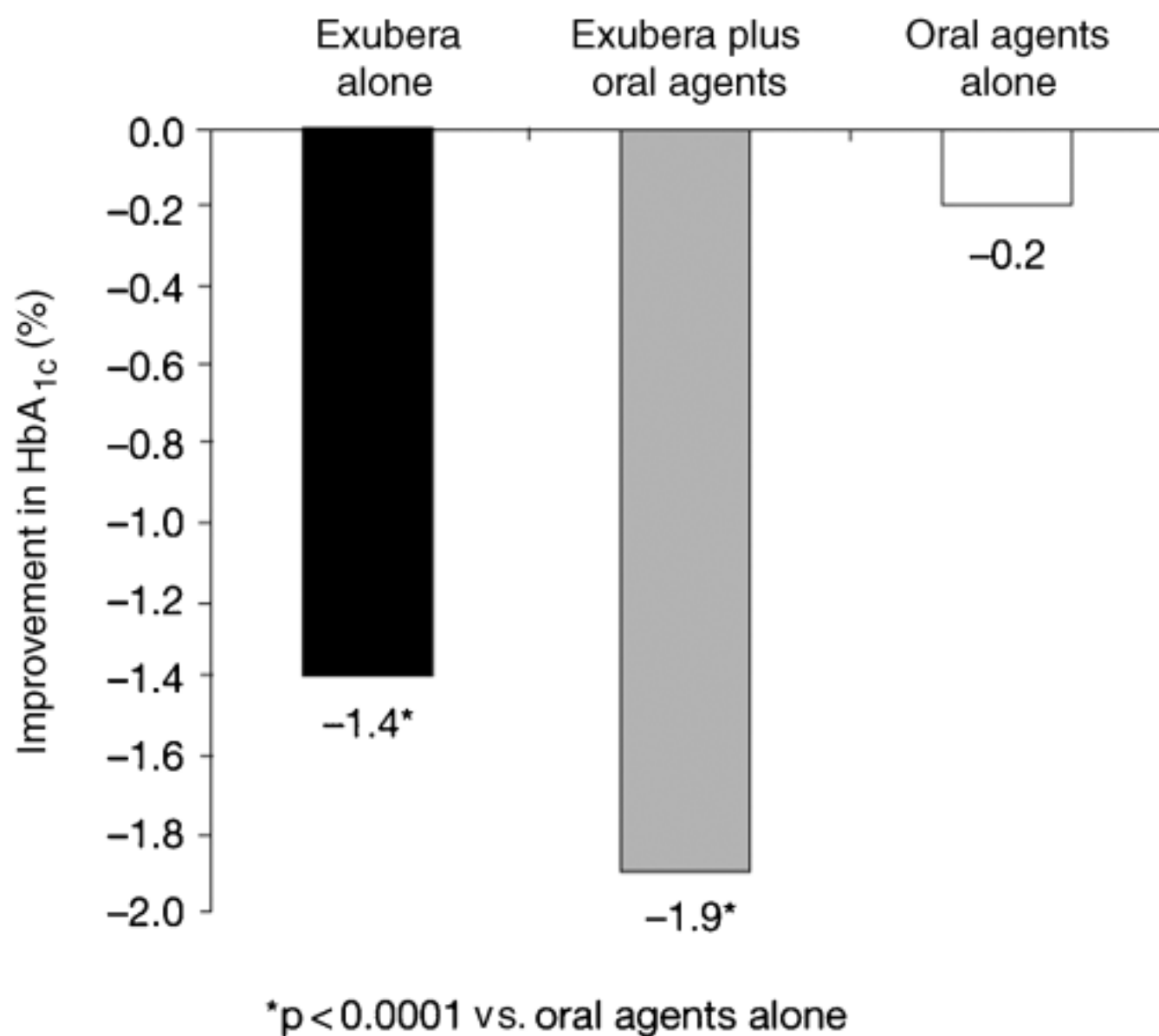


Figure 8 The proportion of patients with type 2 diabetes meeting treatment targets

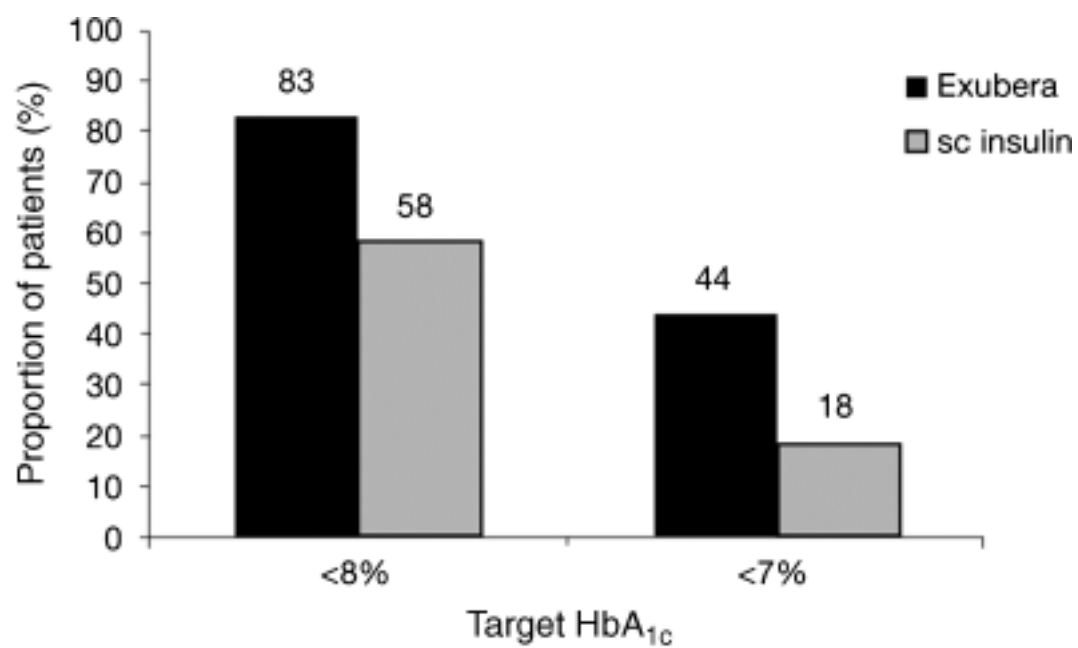


Table 1 Summary of data from Exubera Phase III studies

<i>Study</i>	<i>Patients (n)</i>	<i>Fasting plasma glucose (mmol/l)</i>	<i>HbA_{1c} (%)</i>	<i>Proportion of patients (%) with HbA_{1c} < 7%</i>
Type 1 diabetes				
Skyler (19)	328	−1.9*	−0.3	23.3
Quattrin (20)	335	−1.7	−0.2	15.9
Type 2 diabetes				
Rosenstock (21)	105	−2.4*	−1.4	16.7
Bergenstal (22)	145	Not available	−2.3	44.0
Belanger (23)	299	Not available	−0.7	46.9
*2-h post-prandial glucose.				

Table 2 Summary of pulmonary function test data from Exubera studies

	Mean treatment difference (Exubera – subcutaneous insulin)	
Study	Forced expiratory volume in 1 s (FEV₁;L)*	Diffusion capacity (DL_{co}) (ml/min/mmHg)*
Type 1 diabetes		
Skyler (19)	–0.043 (CI –0.088, 0.003)	–0.819 (CI –1.491, –0.147)
Quattrin (20)	–0.032 (CI –0.085, –0.021)	–1.303 (CI –2.030, –0.577)
Type 2 diabetes		
Rosenstock (21)	–0.002 (CI –0.064, 0.061) vs. orals; –0.028 (CI –0.091, 0.035) vs. orals and inhaled insulin	–0.388 (CI –1.319, 0.542) vs. orals; –0.303 (CI –1.238, 0.633) vs. orals and inhaled insulin
Belanger (23)	–0.015 (CI –0.063, 0.034)	–0.808 (CI –1.574, –0.043)
CI, confidence interval.		