An Assessment of Eligibility for Inhaled Insulin (Exubera)

The Fremantle Diabetes Study

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The product information (1) for human insulin inhalation powder (Exubera; Pfizer) recommends spirometry at baseline, 6 months postinitiation, and at least annually thereafter. Patients with a forced expiratory volume in the first second (FEV_1) <70% of that predicted for age, sex, and height should not start Exubera. In those exhibiting ≥20% decline in FEV_1 during follow-up, Exubera should be discontinued. Exubera is contraindicated for patients with unstable or poorly controlled lung disease, and its efficacy and safety have not been established for patients with asthma or chronic obstructive pulmonary disease. To determine the proportions and characteristics of patients predicted to fall into these categories, we analyzed spirometric and other data from the representative community-based Fremantle Diabetes Study (FDS) (2).

RESEARCH DESIGN AND METHODS — The FDS was a longitudinal observational study involving 127 type 1 and 1,294 type 2 diabetic patients from a population of 120,097 in the state of Western Australia (2). Between May 1993 and September 1994, we performed spirometry on 70 type 1 and 647 type 2 diabetic patients (55 and 50% of all type 1 and type 2 diabetic FDS subjects, respectively). We had additional data from 107 nonsmoking Europid type 2 diabetic patients with no history of chronic respiratory disease who were restudied a mean ± SD 7.0 ± 0.5 years later. Aspects of the data from the type 2 patients have been previously reported (3,4).

Spirometry was performed according to American Thoracic Society standards (3–5). Each subject provided ≥3 acceptable tracings from which standard lung function parameters were measured (corrected for body temperature, air pressure, and water saturation) (6,7).

RESULTS — The 70 type 1 diabetic patients were aged 43.8 ± 15.7 years, and 51% were males. They had a median (interquartile range) diabetes duration of 12.8 years (4.9–23.0) with an A1C of 8.5% (7.9–10.0) (all $P \geq 0.08$ vs. the 57 type 1 diabetic patients without spirometric data). Applying Exubera contraindications (1), 16 smokers and 7 nonsmokers with FEV_1 <70% would be ineligible, which would leave 67% of the original sample. A further four patients self-reporting chronic respiratory disease might also be ineligible, which would reduce this figure to 61%.

The 647 type 2 diabetic patients were aged 63.5 ± 11.1 years, and 50% were male with a median diabetes duration and A1C of 4.0 years (interquartile range 1.4–10.0) and 7.6% (6.5–8.9), respectively. Compared with the type 2 diabetic patients without spirometric data, this group was a mean 1.3 years older, had diabetes for 0.3 years longer, and had an A1C that was 0.3% lower ($P \leq 0.039$) but contained a similar proportion of male subjects ($P = 0.32$). Exclusion of 102 smokers and 91 nonsmokers with FEV_1 <70% would leave 70% of the original sample, and excluding the 30 remaining with chronic respiratory disease would reduce this to 65%. Of these patients, just over half (57%) were treated with insulin and/or oral hypoglycemic agents but still had an A1C above the generally accepted target of 7.0% (8).

The 107 prospectively studied type 2 diabetic patients had a mean age of 61.7 ± 8.6 years, and 48% were male. Their median diabetes duration and A1C was 2.6 years (interquartile range 0.7–7.0) and 7.3% (6.3–8.5), respectively (all $P \geq 0.10$ vs. similar available patients at follow-up without spirometric data). The percentage of these patients with baseline FEV_1 >70% who subsequently developed FEV_1 ≤70% was 12.5% (1.8% per year). In a further 17.3%, there was a fall of >20% in FEV_1 during follow-up (2.5% per year). We have used these rates to estimate the percentage of patients who would become ineligible for Exubera over time (Fig. 1). Assuming stable proportions of smokers and those with chronic respiratory disease, this estimate would increase from 35 to 65% over 7 years.

CONCLUSIONS — Based on smoking history and spirometry, our data suggest that appropriate screening would exclude approximately one-third of community-based type 1 and 2 diabetic patients from Exubera therapy. Since there will be understandable concern with prescribing Exubera for any patient with chronic lung disease, Exubera could be considered inappropriate in ~40% of all diabetic patients. Our type 2 diabetes longitudinal data suggest that this proportion would increase to two-thirds after another 7 years. Under the assumptions made, this increase is due to a decline in FEV_1 (3,9,10) that is strongly related to glycemic exposure (4). We did not follow up the type 1 diabetic patients, but, given our cross-sectional findings and those of

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Abbreviations: FDS, Fremantle Diabetes Study; FEV_1, forced expiratory volume in the first second.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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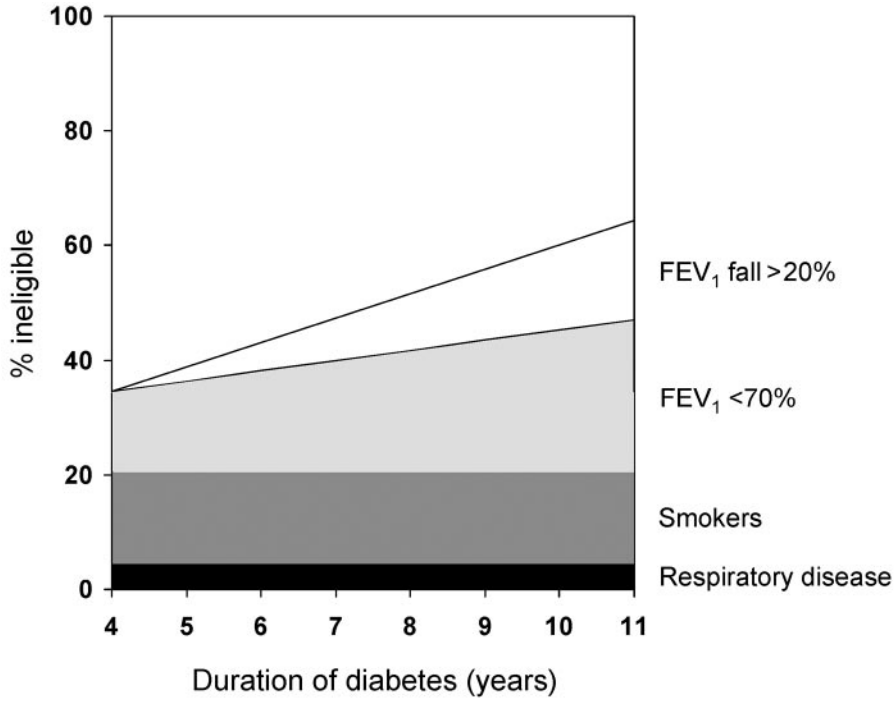

Figure 1—*Schematic representation of the percentage of type 2 diabetic patients ineligible for Exubera therapy between 4 and 11 years disease duration. Data are from cross-sectional and longitudinal FDS sources. The individual contraindications or precautions to Exubera use are represented by the shaded areas.*

other prospective studies (1,9), a similar course seems likely. Based on eligibility and treatment modality data, as well as the proportion with A1C ≥7.0%, only about one-third of our type 2 diabetic patients had a reasonable indication for Exubera at baseline.

Exclusion of all patients with chronic lung conditions may mean that we have overestimated ineligibility. However, criteria for unstable or poorly controlled lung disease are not specified (1), and the lack of efficacy data would justify a cautious approach. In other respects, the present ineligibility estimates appear conservative. For example, compared with U.S. data (11), our type 2 diabetic sample had a lower proportion of smokers (17 vs. 23%). In addition, there would be a minor acute therapy-related FEV_1 fall (1), which would further decrease the proportion in whom Exubera could be prescribed.

The significant proportion of ineligible subjects at initial assessment, and its doubling over the ensuing 7 years, reinforces the need for regular review of Exubera-treated patients (including recommended spirometry). We did not measure gas transfer. Although access to this investigation may be limited by availability and cost, it is recommended as part of initial and continued assessment. A percentage similar to FEV_1 (1) of predicted cut points for carbon monoxide diffusing capacity is likely to add to the proportions of patients who should not be prescribed or continued on Exubera.

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