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Symptoms and pulmonary function in asthma

S. M. ALCOCK, M. MAMUN*, R. J. PRESCOTT† AND C. K. CONNOLLY*

Departments of Medicine, Darlington Memorial Hospital NHS Trust
**University of Newcastle upon Tyne,*
†Medical Statistics Unit, University of Edinburgh

The relationship between symptoms and pulmonary function in asthma is important if the latter is to be held relevant to management guidelines and their audit. Associations between reported symptoms, pulmonary function and therapy were studied in 824 asthmatics (mean FEV_1 75·4% predicted; best FEV_1 84·6% predicted; and actual/best peak flow (PEF) 87·5%). Bronchodilator usage (reflecting symptomatic wheeze) was evenly distributed up to eight times daily; 22·5% of subjects had nocturnal disturbance and 46·3% persistent daytime symptoms. The univariate relationships between symptoms and function were generally closer with best rather than actual/best. They were further explored using quintiles of function. Symptoms were consistently less as best function increased, but were highly significantly greater in the fifth than in the third and fourth quintiles of actual/best FEV_1. There was a trend to a similar U-shaped relationship of actual/best PEF with nocturnal disturbance and daytime symptoms. Best function is a good determinant of expected symptom load in an asthmatic population. Below 85% actual/best function reflects the prevalence of symptoms. In asymptomatic patients a level of at least 85–90% is a useful check of physiological control but will not exclude some symptomatic patients, irrespective of best function.

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Introduction

Published guidelines suggest that measurements of pulmonary function should be incorporated in the management of chronic asthma (1,2). Assessments should be made in the light of best function (3). If guidelines and audit of outcome are to be relevant to management, particularly from the patient's point of view, then any measure of pulmonary function is likely to be most useful if it bears some relationship to symptoms. However, the relationships between symptoms and measurements of pulmonary function in patients with airway obstruction are difficult to establish and, even with the best objective measures of performance, pulmonary function explains less than 50% of between-patients variance in symptom scores (4,5).

In the Darlington and Northallerton long-term asthma study (DANLAST) we have determined best function on optimal therapy in all subjects and assessed control at the time of attendance by the actual function observed divided by the best obtainable (6). In cross-sectional models, we observed a steep decline in best function with increasing therapeutic step and that therapy may be adjusted to obtain similar levels of actual/best function at each therapeutic step (7). Similar results were seen in an audit study involving several centres (8).

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Correspondence should be addressed to: C. K. Connolly, Darlington Memorial Hospital, Hollyhurst Road, Darlington DL3 6HX, U.K.

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In the tenth-year review of DANLAST, all current subjects were reviewed and new patients entered. In the preliminary longitudinal analysis, poor best function predicted mortality, but after multivariate analysis, actual/best function was a poor predictor of long-term outcome (9). We also recorded current symptoms in both the subjects under review and the new entrants. As we confirmed that best function was worse in those on a higher therapeutic step, we anticipated an association between symptoms, particularly those with a global connotation, and best function, but also anticipated a strong relationship between actual/best function and current symptoms. In order to test this hypothesis, we looked at the relationship between reported symptoms, pulmonary function (expressed as best and actual/best), and therapy in all participants.

Methods

SUBJECTS

All patients aged over 18, attending with a clinical diagnosis of asthma at hospital clinics or privately in the former Darlington and Northallerton Health Districts of the National Health Service were included, subject to the following criteria:

A clinical diagnosis of asthma;
Demonstration of reversibility of peak flow (PEF) by $\geq 15\%$ to $\geq 200\,l\,min^{-1}$ on more than one occasion at some time in the past;

TABLE 1. Details of subjects and their pulmonary function

	Male	Female	All
n	405	419	824
Age (years) (SD)	55·8 (15·01)	54·2 (16·4)	55·0 (15·8)
Atopic (%)	186 (45·9)	188 (44·9)	374 (45·3)
Current smokers (%)	30 (7·4)	32 (7·6)	62 (7·5)
Never smokers (%)	119 (29·3)	213 (50·8)	332 (40·3)
Best PEF % (SD)	86·3 (18·7)	102·3 (21·0)	94·5 (21·4)
Actual/best PEF % (SD)	87·4 (12·1)	87·7 (12·3)	87·5 (12·1)
Best FEV_1 % (SD)	80·4 (27·8)	88·4 (24·3)	84·6 (26·3)
Actual/best FEV_1 % (SD)	90·0 (11·6)	89·3 (11·6)	89·6 (11·6)

TABLE 2. Pulmonary function showing mean and interquintile values

				Interquintile values			
	n	Mean	SD	1	2	3	4
Actual FEV_1	751	75·4	26·8	49·1	68·3	82·3	98·3
Best FEV_1	757	84·6	28·6	60·3	79·0	92·0	107·3
Actual/best FEV_1	751	89·6	11·4	81·0	88·8	94·2	98·2 109·6
Actual PEF	815	83·5	24·1	60·5	79·3	90·5	103·5
Best PEF	824	94·5	21·4	76·1	90·4	101·0	111·9
Actual/best PEF	815	87·5	12·1	78·4	87·7	93·3	98·0

TABLE 3. The therapeutic steps of the subjects, showing the percentage distribution of those on satisfactory therapy. (Subjects on booster steroids at attendance are classified by their normal preventative treatment.)

Therapy	Male (*n*=405) n (% satisfactory)	Female (*n*=419) n (% satisfactory)	All (*n*=824) (% satisfactory)
Bronchodilator only/DSG	39 (10·4)	38 (9·7)	77 (10·1)
Inhaled steroids <800 μg	136 (36·2)	167 (42·3)	303 (39·6)
Inhaled steroids 800–1000 μg	119 (31·7)	85 (21·8)	204 (26·6)
Inhaled steroids >1000 μg	52 (13·9)	66 (16·9)	118 (15·4)
Oral steroids	29 (7·7)	35 (9·5)	64 (8·4)
All satisfactory	375	391	766
Not satisfactory	30 (7·4)*	28 (6·7)*	58 (7·0)*
All patients	405	419	824

*Percentage of all subjects.

Previous attendance of at least 1 year.

The study started in 1983, with reviews in 1988–1989 and 1993–1994. New subjects satisfying the above criteria were entered at each review. Patients who had been discharged or lost to follow-up in the intervening period were offered a special attendance solely for the study. This report includes the findings recorded during the tenth year of the study in all subjects, whether current clinic attenders, special attenders or new entrants.

HISTORY

A structured history was taken, which included the following:

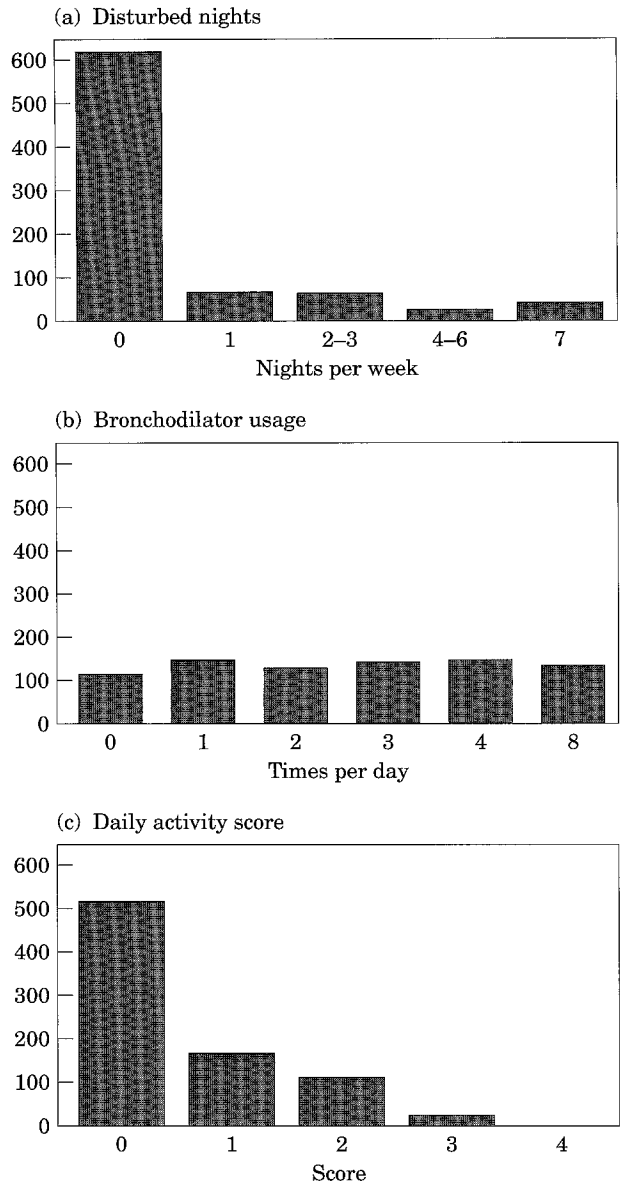

FIG. 1. The distribution of symptom scores: (a) disturbed nights; (b) bronchodilator usage; (c) daily activity score.

(a) Bronchodilator usage: average frequency (occasions) of short-acting bronchodilator use per 24 hours over the previous 4 weeks
(b) Nocturnal disturbance: average number of nights disturbed per week by respiratory symptoms over the previous 4 weeks
(c) Daily activity score: 0=normal; 1=coped despite symptoms; 2=activities, games etc. restricted because of symptoms; 3=unable to do normal household activities because of symptoms; 4=severely disabled (e.g. assistance required with dressing, wheelchair, etc).

THERAPEUTIC REGIMEN

Patients who had been maintained on the same mutually agreed treatment for 3 months were regarded as being on satisfactory treatment. Treatment was divided into the following steps, using solely prophylactic medication:

A Bronchodilator, including DSG;
B Inhaled steroids, <800 μg;
C Inhaled steroids, 800–1000 μg;
D Inhaled steroids, >1000 μg;
E Oral steroids;
U Unstable.

PULMONARY FUNCTION

Both PEF (Clement Clarke) and FEV_1 (Vitalograph, Maidenhead, UK) were measured at attendance. No specific instructions were given with regard to withholding bronchodilator before the attendance. Actual function was that recorded. Best function was established according to protocol (8), being the highest value recorded since 1 January of the previous year:

If actual function >80% predicted: after bronchodilator;
If 70–80% predicted: on regular suppressive medication, with twice daily PEF recording for $\geq$5 days;
If <70% predicted: after $\geq$5 days of oral prednisolone (30 mg/day) with twice daily recording of PEF.
Actual and best function were expressed as per cent predicted [Cotes (10)] and actual/best function as a percentage.

TABLE 4. The relationships between symptoms and parameters of pulmonary function as independent variables. The Spearman rank correlation coefficient and probabilities are shown (probability is 0·0001 except where shown)

	PEF			FEV_1			FVC
	Actual	Best	Actual/best	Actual	Best	Actual/best	Best
Bronchodilator usage	0·38	0·33	0·24	0·39	0·36	0·12	0·28
Nocturnal disturbance	0 18	0·14 (P=0·0002)	0·16	0·18	0·16	0·04 (P=0 20)	0·15
Activity score	0·41	0·37	0·25	0·42	0·42	0·08 (P=0·02)	0·38

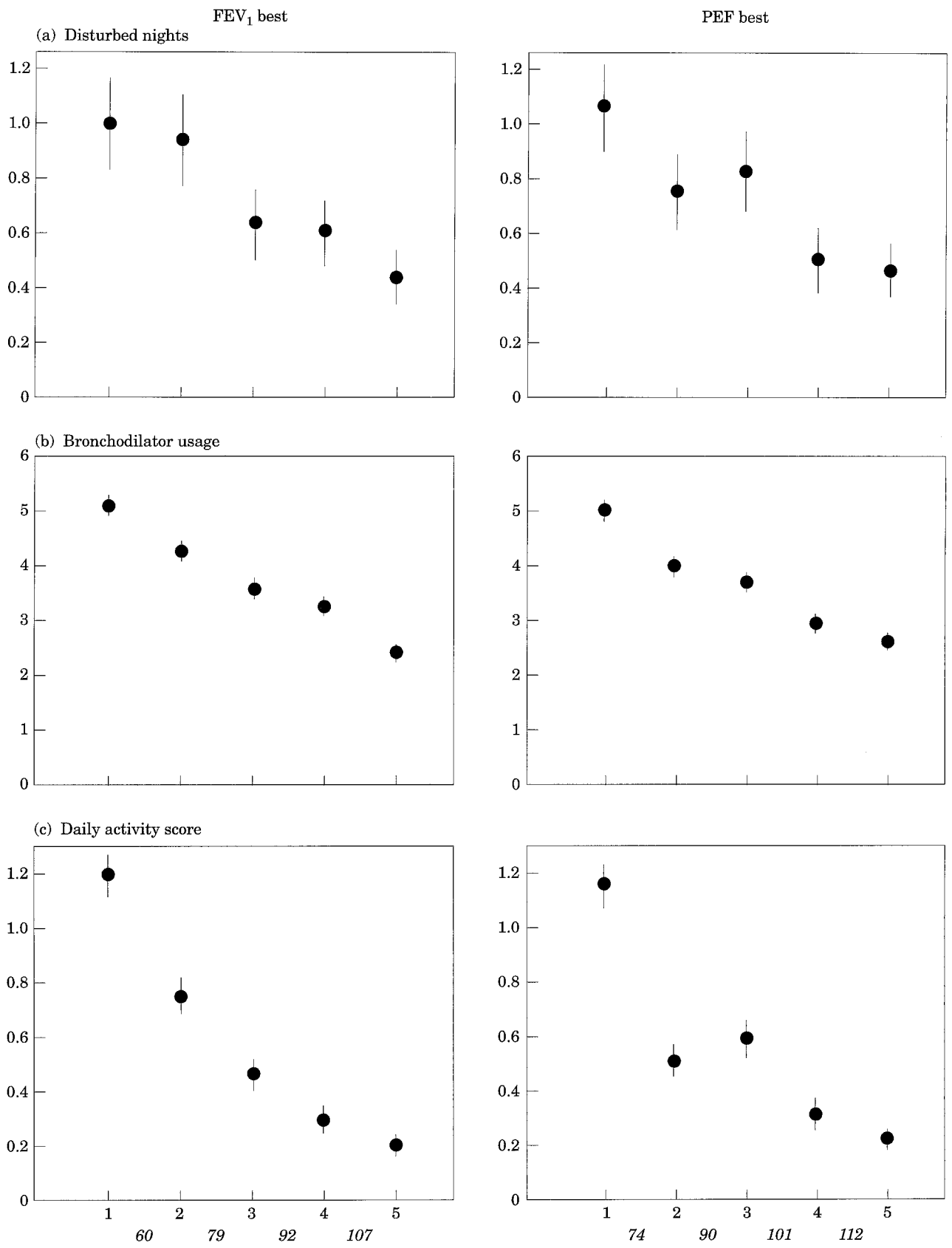

FIG. 2(a). Symptom scores (SEM) by quintile of pulmonary function: best.

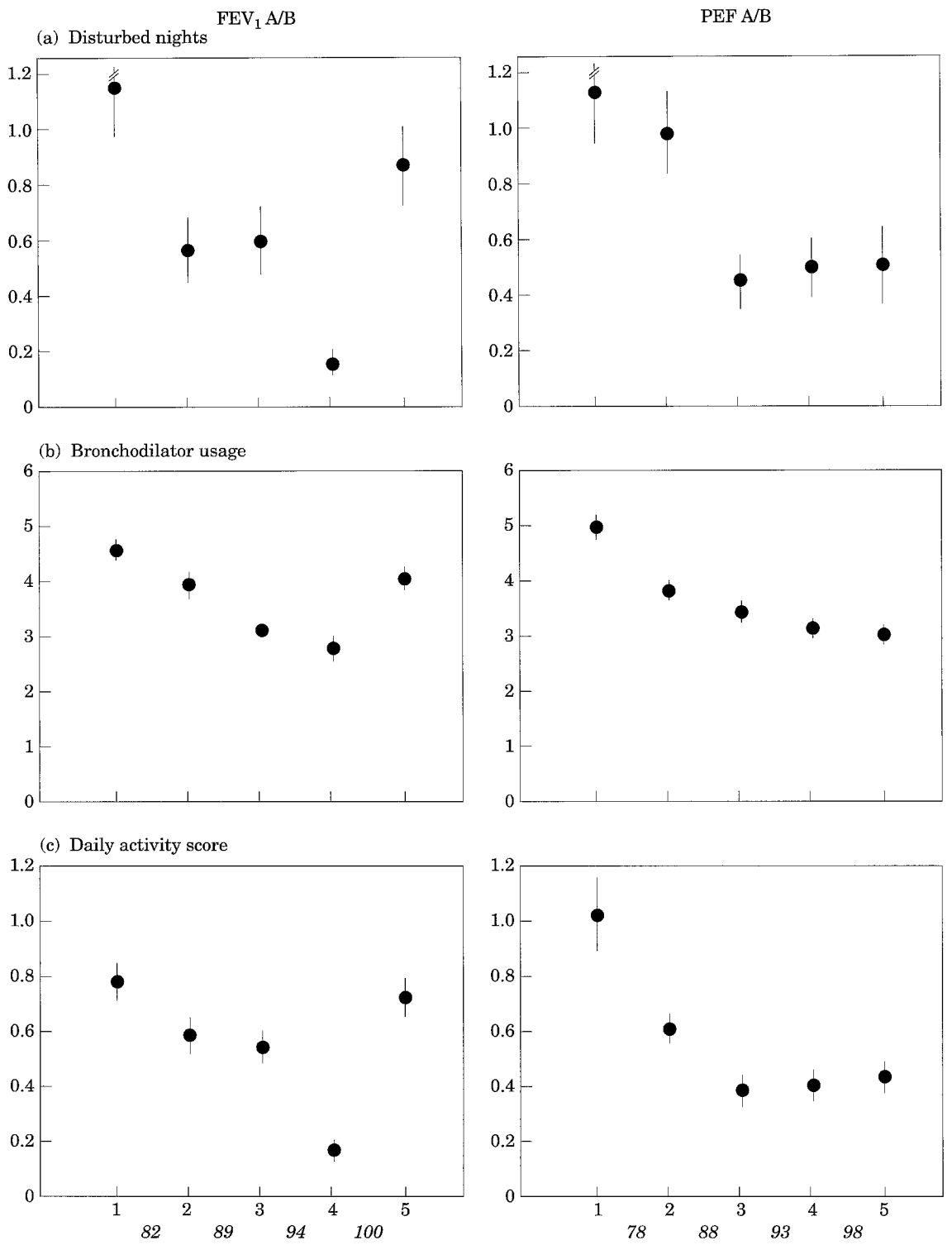

FIG. 2(b). Symptom scores (SEM) by quintile of pulmonary function: actual/best.

STATISTICAL METHODS

The statistical methods used are either descriptive or are standard statistical methods. The methods used are reported as they occur in the Results section. All calculations were performed using version 6.04 of SAS/PC.

Results

GENERAL

The demographic details are shown sex-specifically in Table 1 and pulmonary function in Table 2. Although mean best

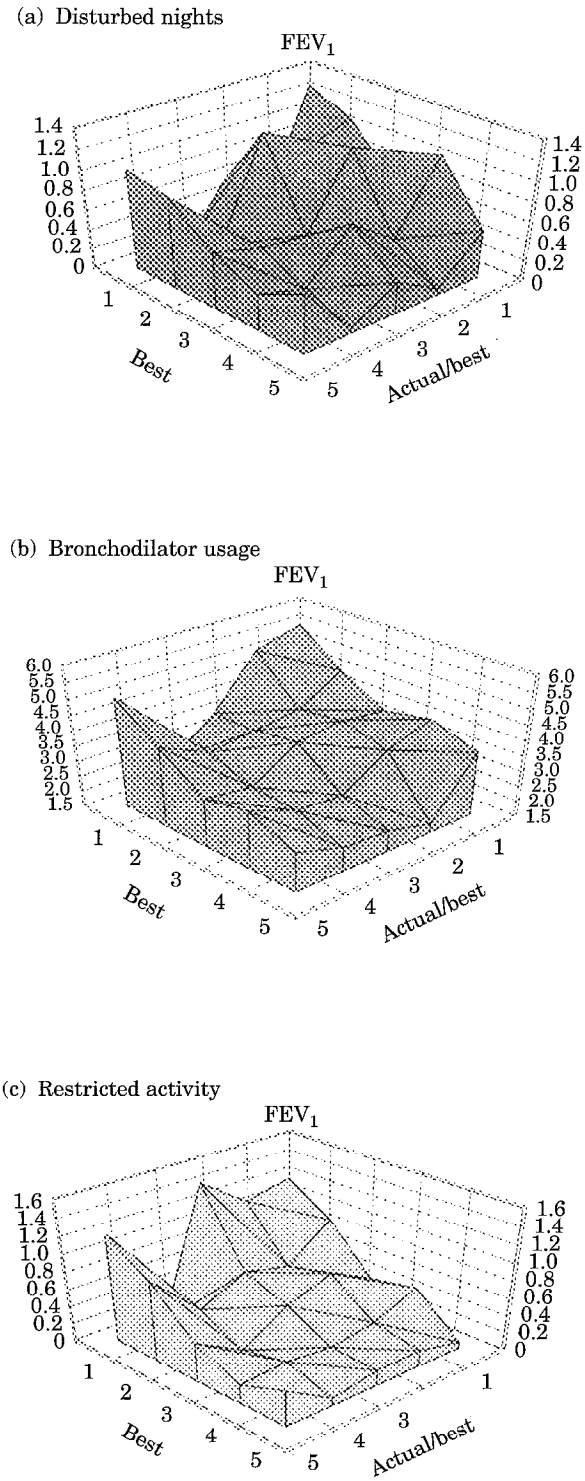

FIG. 3. Symptom scores by quintile (Q) of actual/best FEV_1 stratified by best FEV_1: (a) disturbed nights[1]; (b) bronchodilator usage[2]; (c) daily activity score[3]. Where [1]Q5 *vs* Q4: $\chi^2=14{\cdot}2$, $P=0{\cdot}0002$; Q5 *vs* Q3&4: $\chi^2=9{\cdot}3$, $P=0{\cdot}002$; [2]Q5 *vs* Q4: $\chi^2=18\ 1$, $P=0{\cdot}00002$; Q5 *vs* Q3&4: $\chi^2=21{\cdot}8$, $P<0{\cdot}00001$; [3]Q5 *vs* Q4: $\chi^2=30{\cdot}0$, $P<0{\cdot}00001$; Q5 *vs* Q3&4: $\chi^2=18{\cdot}6$, $P=0{\cdot}00002$. Tests for trend applied throughout.

PEF [male 86·3 (18·7), female 102·3 (± 21·0)] is highly significantly greater in females than in males ($P<0\ 0001$), actual/best FEV_1 [male 90·0 (± 11·6), female 89·3 (± 11·6)] and actual/best PEF [male 87·4 (± 12·1), female 87·7 (± 12·3)] were almost identical. Despite the differences in best function, the relationships between symptoms, function and therapeutic step were similar in males and females, and so the combined results are presented.

THERAPY

The distribution of therapeutic step is summarized in Table 3, the percentage distribution being shown for those on satisfactory maintenance treatment. Mean actual/best peak flow varied from 82% for those on oral steroids to 91% for those on low-dose inhaled corticosteroids. Of the total, 30 (7·4%) males and 28 (6·7%) females were not on satisfactory maintenance treatment.

SYMPTOMS

The distribution of symptoms is shown in Fig. 1. Bronchodilator usage was evenly distributed between virtually no use and more than 8 times a day. Only 22·5% of subjects had nocturnal disturbance; 16·6% had symptoms sufficient to disturb their normal activities and 20·7% claimed to cope despite symptoms.

SYMPTOMS AND PULMONARY FUNCTION (RANK CORRELATION)

There was a highly significant correlation between symptoms score and actual function (Table 4). The relationship with best function was of the same order for all three measurements, but strongest with FEV_1. The relationship between symptoms and actual/best function was much weaker for FEV_1. With PEF the relationship with nocturnal disturbance was similar for best and actual/best function. These results suggest that most of the associations of symptoms with pulmonary function can be explained by best function, particularly when the measure is FEV_1.

Distribution of symptoms by quintiles of pulmonary function

The relationship between symptoms and pulmonary function was explored further by examining symptom mean scores within quintiles of pulmonary function. When symptom scores were plotted against best function, there was a consistent inverse relationship (Fig. 2(a)). In contrast symptoms were highly significantly greater in the fifth quintile of actual/best FEV_1 than either the fourth taken alone, or the third and fourth taken together (see Fig. 2(b)). Although no such significant difference is seen between the fifth and lower quintiles of actual/best PEF, there is little difference in symptoms between the third, fourth and fifth quintiles,

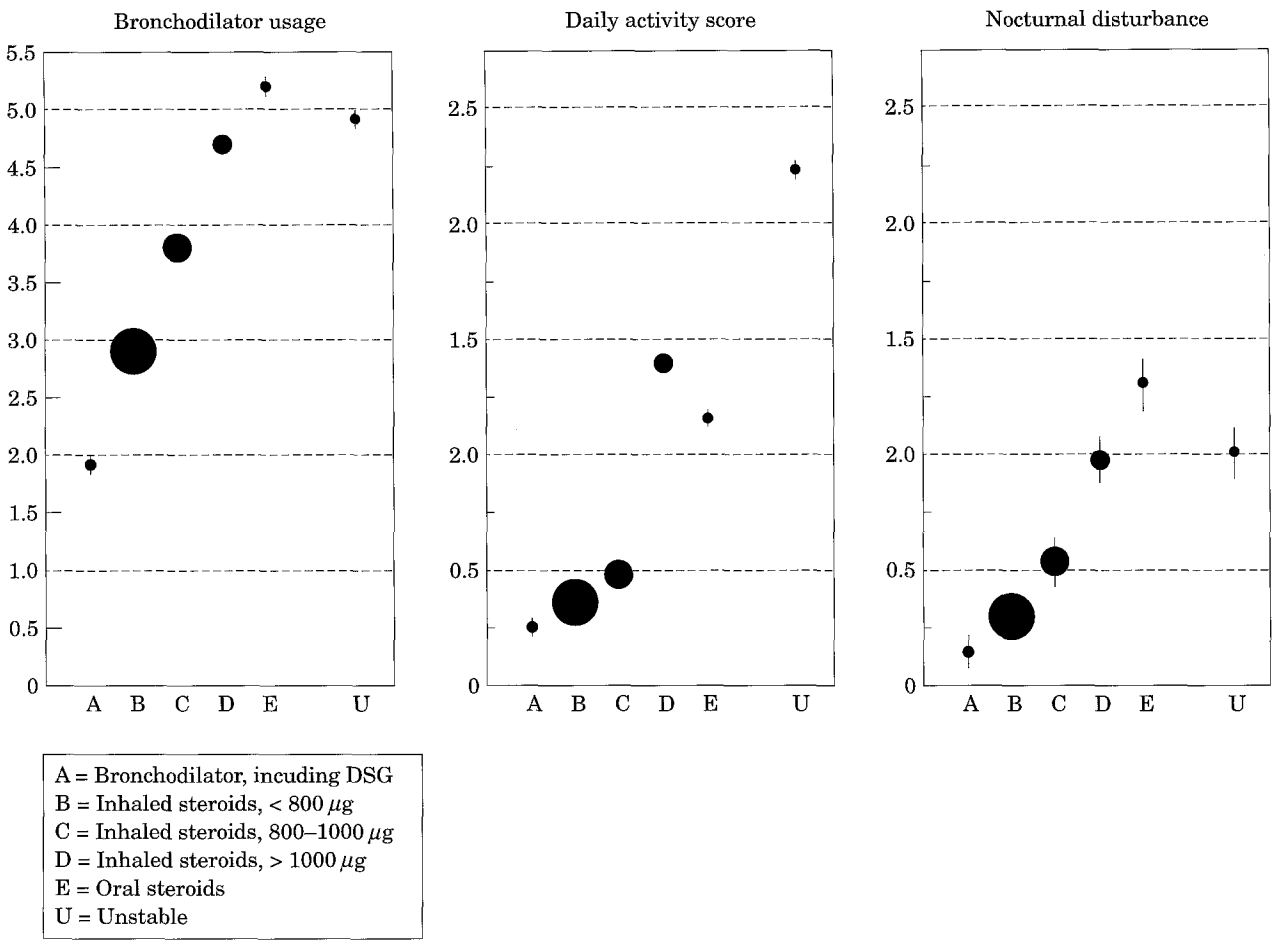

FIG. 4. Symptom scores (SEM) for each treatment step. The size of a point is proportionate to the number of observations. Where SEM is not shown it is less than equal to the radius of the point.

with a U-shaped trend for nocturnal disturbance and daily activity score (Fig. 2(b)).

The relationship between symptoms and actual/best FEV_1 was then stratified by quintiles of best FEV_1. Allowing for small numbers in some of the cells, the relationship between symptoms and actual/best function remains U-shaped, whatever the level of best function (Fig. 3).

SYMPTOMS AND TREATMENT STEP

Restricted activity and nocturnal disturbance increased progressively with symptoms step (Fig. 4). There was less variation with bronchodilator usage. The relationships between symptoms and actual/best function remains U-shaped whatever the level of therapy. This distribution is statistically highly significant (Fig. 5).

Discussion

All subjects included in this study were currently attending in secondary care when they first entered the Darlington and Northallerton long-term asthma study. However, some of the earlier entrants continued to attend hospital at long intervals solely because they had been enrolled. A further group consisted of special attenders, who had been specifically recalled for the study. Although all these asthmatics were severe enough to be referred to hospital at one stage, the group as a whole included more patients with mild to moderate asthma than might be expected in a hospital-based study. They were, on the whole, well controlled, with mean actual/best function above the recommended 80–85% levels (1,2). The incidence of nocturnal disturbance is lower than that reported by Turner-Warwick (11). If the frequency of bronchodilator usage that requires adjustment of therapy is taken more than twice daily, then recorded bronchodilator usage was disappointing. Despite this, most subjects claimed little, if any, effect on their daily activity.

Asthma was a clinical diagnosis supported by compatible reversibility of peak expiratory flow. Asthma and chronic obstructive pulmonary disease (COPD) were not regarded as mutually exclusive. Indeed, one of the purposes of the long-term study in which all these subjects participate is to investigate the development of COPD, as defined by best function, in an asthmatic population. We have previously observed that best function is more closely associated with therapeutic step than is actual/best. We hypothesized that

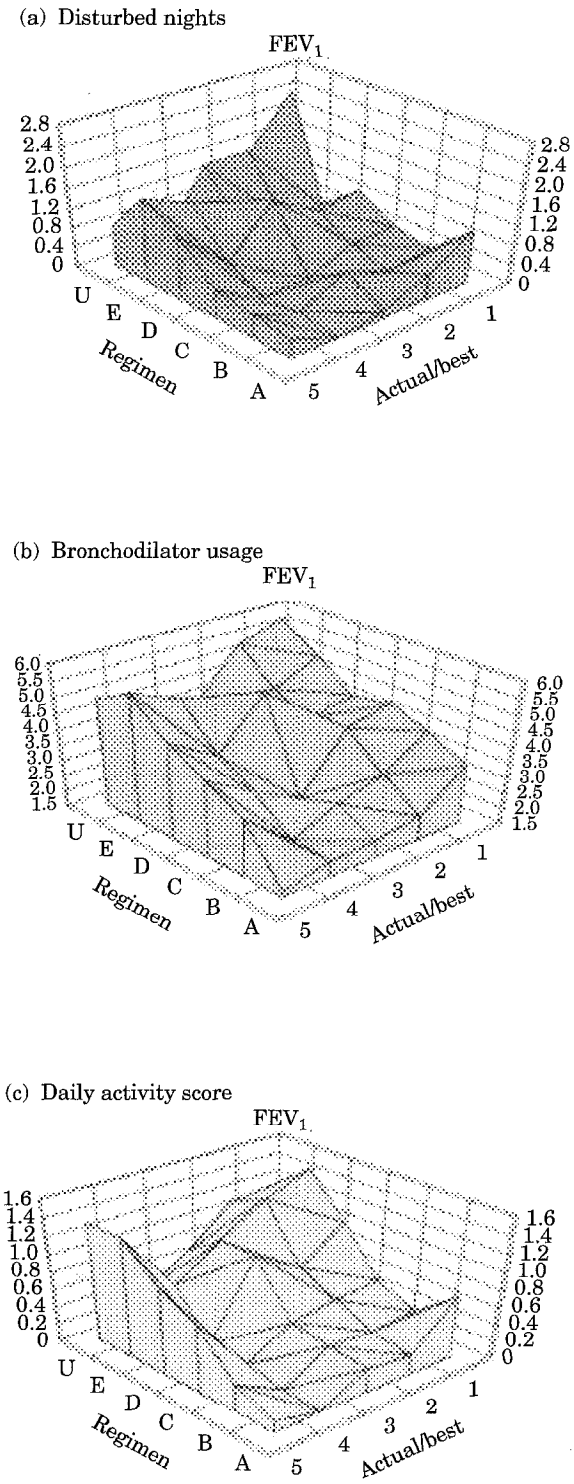

FIG. 5. Symptom scores by therapeutic step stratified by actual/best FEV_1: (a) disturbed nights; (b) bronchodilator usage; (c) daily activity score.

this would also apply to symptoms, but the contribution of actual/best function might be relatively much greater. The results confirm a highly significant relationship between the level of obstruction and symptoms observed at attendance. The strongest relationship was with restricted activity, followed by bronchodilator usage. The association with nocturnal disturbance was much weaker. All three estimates of best function (PEF, FEV_1 and FVC) showed similar relationships of the same magnitude and in the same order suggesting that best function is the principal determinant of symptoms. This is a striking observation considering that if 85% of predicted is taken as the lower limit of normal, 50% of subjects did not show persistent obstruction as judged by FEV_1 and 70% as assessed by best PEF. This is in keeping with the finding that the association between mortality and best function observed in DANLAST is not restricted to those whose post bronchodilator function is outside the normal range. There is a close association between best function and therapeutic step (8) and we have now shown a similar association between symptoms and therapeutic step.

It is clearly unrealistic to expect therapy to suppress symptoms below the level associated with best achievable function. Nevertheless, it was anticipated that there would be a relationship between actual/best function and symptoms, independent of therapeutic step and best function. The target level for actual/best function (85%) was independent of actual/best function and the same at each therapeutic step. This reduces the chances of demonstrating a relationship between symptoms and actual/best function. In practice, median actual/best was above target in all but the high-dose inhaled and oral steps, representing only 22% of subjects. Provided that the fortieth centile was achieved there is no further advantage. Fewest symptoms were reported in those whose actual/FEV_1 at attendance was just below 100% of their best. During follow-up in our clinics, actual/best function is regarded as a measure of what the patient regards as satisfactory, rather than a diagnostic tool, so bronchodilator usage is not restricted before attendance. It follows that the recent use of rescue medication by subjects symptomatic immediately before attendance is the most obvious explanation as to why those achieving near maximal function clinic had more symptoms than those at slightly lower levels. However, there are several other factors that might contribute to the U-shaped relationship between symptoms and actual/best function. Symptomatic patients on long-acting bronchodilators, particularly when used to control nocturnal disturbance, may have no reversible airflow obstruction at attendance, and so will appear to be well controlled. Other patients may have developed persistent obstruction which had become fixed, explaining why patients in the worst quintile of best function but in the best quintile of actual/best function tended to be particularly symptomatic. Symptomatic patients with normal best and actual/best function may include those with sudden unpredictable but beta-agonist-reversible wheeze, and others whose expectations are unrealistically high. It is also possible that patients whose bronchial lability is not totally suppressed may eventually have least symptoms because of appropriate avoidance of sensitizers and non-specific irritants. In the longitudinal analyses of this study, in the 5- and 10-year periods up to 1993, the patients in the third quartile (range 90–95%) of actual/best function at entry had the lowest mortality (9,12).

It was confirmed that patients with most symptoms do have poorest actual/best function, but that a proportion of patients with acceptable actual/best function at attendance are also symptomatic. The results suggests that actual/best function of at least 85–90% is a useful check in those who claim to have good control, provided it is accepted that high values, particularly when approaching 100%, will not exclude the possibility of important symptoms. In the longer term, the strong associations between symptoms and best function even within the normal range suggest that the benefit of present relieving therapy will always be limited, unless methods can be found to reverse currently irreversible disease. Recent studies are beginning to suggest that early and appropriate use of inhaled corticosteroids may prevent its development (13,14).

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References

1. British Thoracic Society, British Paediatric Association, Royal College of Physicians of London *et al.* Guidelines on the management of asthma. *Thorax* 1993; **48:** S1–S24.
2. Sheffer AL (Chairman). International consensus report on diagnosis and management of asthma. *Clin Exp Allergy* 1992; **22:** Suppl. 1.
3. The British Thoracic Society, The National Asthma Campaign, The Royal College of Physicians *et al.* The British Guidelines on Asthma Management: 1995 Review and Position Statement. *Thorax* 1997; **52** (Suppl. 1): S1–S21.
4. Butland RJA, Pang J, Gross GR, Woodcock AA, Geddes DM. Two, 6 and 12 minute walking tests in respiratory disease. *Br Med J* 1982; **284:** 1607–1608.
5. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992; **47:** 1019–1024.
6. Connolly CK, Chan NS, Prescott RJ. The relationship between age and duration of asthma and the presence of persistent obstruction in asthma. *Post Grad Med J* 1988; **64:** 422–425.
7. Connolly CK, Prescott RJ. Pulmonary function and drug regimens in asthmatics. *Br J Clin Prac* 1990; **44:** 148–153.
8. Connolly CK, Prescott RJ, Alcock SM, Gatnash AA. Actual over best function as an outcome measure for asthma. *Respir Med* 1994; **88:** 453–459.
9. Connolly CK, Roy PM, Alcock SM, Prescott RJ. The Darlington and Northallerton Asthma Study: morality at ten years. *Eur Resp J* 1995; **8:** 316s.
10. Cotes JE. *Lung Function,* 4th ed. Oxford: Blackwell, 1978.
11. Turner-Warwick M. Nocturnal asthma: a study in general practice. *J R Coll Gen Pract* 1989; **39:** 239–243.
12. Connolly CK, Alcock SM, Roy PM, Prescott RJ. Darlington and Northallerton asthma study: mortality 1988/93. *Am J Respir Crit Care Med* 1996; **153:** A867.
13. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; **88:** 373–381.
14. Haahtela T, Jarvenin M, Kava T, Kiviranta K, Koskinen S, Lethonen K *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994; **331:** 700–705.