

Measurement characteristics of two asthma symptom diary scales for use in clinical trials

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Measurement characteristics of two asthma symptom diary scales for use in clinical trials. N.C. Santanello, B.L. Barber, T.F. Reiss, B.S. Friedman, E.F. Juniper, J. Zhang. ©ERS Journals Ltd 1997.

ABSTRACT: The measurement characteristics of two asthma symptom diary scales developed for use as health outcome measures in clinical trials of asthma therapy were investigated.

A daytime diary scale was designed to capture the frequency and inconvenience of daytime asthma symptoms and their effects on activities, and a nocturnal asthma symptom diary scale was designed to capture awakenings with asthma symptoms. The internal consistency, reliability, validity and responsiveness of both asthma diary scales were assessed in 346 adult asthma patients in two placebo-controlled clinical trials of an investigational asthma therapy, a leukotriene biosynthesis inhibitor.

The daytime symptom scale showed sufficient internal consistency (0.90–0.92), and the daytime and nocturnal symptom scales showed sufficient test retest reliability (0.69–0.87). Construct validity was demonstrated by generally moderate-to-strong correlations for changes in the diary scales with changes in other measures of asthma status, such as forced expiratory volume in one second (FEV₁), peak expiratory flow (PEF), and puffs of β -agonist inhaler. Both scales demonstrated significant responsiveness to change in asthma due to therapy in one of the clinical trials.

Based on these results, the daytime and nocturnal asthma symptom diary scales show measurement characteristics appropriate for use as asthma outcome measures in clinical trials of asthma therapy.

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Health outcome measures, such as patient-reported asthma symptoms, use of β -agonist inhaler, and asthma-specific quality of life [1, 2], are important measures of clinical status in asthma. These are used in addition to objective measures of airway function, such as spirometry (forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC)) measured in a clinical setting, and peak expiratory flow (PEF) measured at home with a handheld PEF meter. Both periodic questionnaires and daily diaries have been used in asthma clinical trials to record change in patient-reported asthma symptoms and their effects on activities [3–10]. However, few of these asthma questionnaires or diaries have been subjected to critical scientific assessment to determine their validity as a health outcome measure [10].

Recording symptoms on a daily diary captures day-to-day variability in asthma and reduces the likelihood of recall bias [11]. Therefore, for our clinical trials, we chose to characterize weekly asthma symptom burden by averaging daily asthma symptoms captured in a diary, rather than using asthma symptom questionnaires that are administered weekly or monthly. We developed and validated two daily asthma symptom diary scales to briefly capture change in patient-reported measures of asthma over the course of a therapeutic asthma intervention. A

daytime diary scale evaluated daytime symptoms, and a nocturnal diary scale evaluated awakenings with asthma symptoms.

The diary scales were assessed in two clinical studies of an investigational asthma drug, a leukotriene biosynthesis inhibitor that binds to the 5-lipoxygenase activating protein. Patients recorded twice daily PEF measurements and β -agonist inhaler use, concurrently with the symptom scales, in a daily diary. This assessment included determining the measurement characteristics of the diary scales, that is: internal consistency; test retest reliability; longitudinal construct validity; and, finally, critical for an instrument which is designed to evaluate change in disease over time, responsiveness. This report describes the daytime and nocturnal asthma symptom diary scales and presents their measurement characteristics as determined in two clinical studies.

Methods

Subjects

Study participants were adult patients 18–65 yrs of age, with mild-to-moderate asthma, who were evaluated

in two separate clinical studies, between September 1992 and December 1992. Patients were volunteers recruited from asthma clinics. Patients were required to have a history of typical, recurring symptoms of asthma, a FEV₁ 40–80% of predicted, and evidence of reversibility of airway obstruction after inhaled β -agonist (at least 15% increase in the FEV₁ absolute value). Furthermore, all patients gave informed consent and were required to be able to complete daily symptom diaries and perform pulmonary function tests (FEV₁, FVC and PEF) in a consistent manner.

Study design

Data for this report were collected from two separate clinical studies of asthmatics. The studies consisted of two clinical trials (referred to as clinical trials A and B). Both studies were placebo-controlled studies using an investigational asthma drug. Patients were allowed use of β -agonist inhalers on an as needed basis. Both clinical trials included a 3 week placebo run-in period and a 2 week wash-out period. Patients in clinical trial A were randomized, to one of four different doses of active treatment or to placebo in the 6 week double-blind treatment period. Thirty two percent of patients, who were taking theophylline at the beginning of the placebo run-in period, were allowed to continue using the same dose throughout the trial. Clinical trial B had a 4 week double-blind treatment period, comparing one dose of active treatment and placebo; all patients in this study were also taking a fixed dose of inhaled corticosteroids (mean dose 800 $\mu\text{g}\cdot\text{day}^{-1}$).

In both trials, patients completed a daytime diary card at night before going to sleep and a nocturnal diary card on arising in the morning. At weekly clinic visits, patients returned the daytime and nocturnal diary cards and performed standardized pulmonary function tests (FEV₁ and FVC). Both clinical trials were approved by Ethics Boards.

Measurements

The daytime and nocturnal diary cards were developed for use in asthma clinical trials. A group of clinical researchers, with expertise in asthma and epidemiology, constructed the diary questions for the daytime and nocturnal scales (Appendix) based on unvalidated diary scales used in previous trials. The daytime asthma symptom scale captures daytime asthma symptoms with four questions to assess: 1) frequency of general asthma symptoms; 2) inconvenience of asthma symptoms; 3) frequency of limitation during usual activities; and 4) how often asthma symptoms limited ability to perform usual activities. Patients were instructed to circle the appropriate response for each of the four daytime asthma symptom questions before going to sleep for the night. Patients also recorded in the daytime diary card the number of actuations of β -agonist from a metered-dose inhaler (MDI) that were used during the day, and measured and recorded the best of three PEF rates, using a mini-Wright peak flow meter.

The nocturnal symptom scale was developed to evaluate awakenings with asthma symptoms. Patients were

instructed to check the appropriate response to the awakening question, which was completed on arising in the morning and asked if the patient awoke with asthma symptoms during the night or in the morning. The response option "awake all night" was explained to the patient to mean either awake all night with asthma symptoms or occurrence of recurrent episodes of awakenings. In addition, in the nocturnal diary card, the patients recorded the number of actuations of β -agonist from a MDI that were used after going to sleep for the night, and measured and recorded the best of three PEF rates on arising in the morning.

The awakening question was designed to take into account the circadian variation of airway calibre in patients with asthma. Since bronchoconstriction occurs in the early morning hours (the nadir occurs near 06.00 h), the awakening question evaluates the entire overnight period, including symptoms that are present on awakening. Patients were instructed to consider the awakenings that occurred either during sleep or on awakening, and the number of times they used an inhaled β -agonist from bedtime to the time of awakening (defined as prior to arising from bed) when completing the diary in the morning. Patients were asked to perform morning and evening PEF measurements prior to using inhaled bronchodilator.

Data analyses

Scoring of measures. The daytime asthma symptom scale used a range of response categories for each question from 0 to 6, indicating the least to the most asthma symptomatology. The nocturnal diary scale used response categories ranging from 0 (indicating no awakening with asthma symptoms) to 3 (indicating awake all night). Daily daytime scale scores were computed as the average of the four questions on the daytime symptom scale. An overall diary score for the week was computed as the average of the daily daytime scale scores. Weekly average scores for the nocturnal diary scale were computed in a similar manner. A decrease in the weekly score for the daytime and nocturnal scales indicated an improvement in asthma symptoms. The change from baseline in the asthma scale scores was computed as the difference between the average score from the last 2 weeks of the placebo run-in period and the last two weeks of the active treatment phase in the 2 clinical trials.

Measurement characteristics. The asthma diary scales were designed to be evaluative measures, *i.e.* to specifically assess change in asthma over time within a clinical trial. As part of the validation of these evaluative measures, an assessment of the following measurement characteristics was performed: internal consistency, test retest reliability, longitudinal construct validity and responsiveness.

Internal consistency estimates the extent to which each item of a questionnaire or scale is measuring the same construct [12]. Internal consistency was assessed with Cronbach's Alpha. Values of Cronbach's Alpha coefficient greater than 0.70 and less than 0.95 indicate good internal consistency [13]. Internal consistency for the

daytime scale was assessed using the average scores for each of the four questions for the last week of the placebo run-in period. The 95% confidence limits (95% CLs) were calculated using the Jackknife method [14]. Since the nocturnal scale consists of only one question, an assessment of internal consistency is not applicable.

The test retest reliability of the diaries was assessed with the intraclass correlation coefficient (ICC) [15], which measures the proportion of the variability in the scores between subjects. An ICC of 0.75 and above is considered acceptable for a research instrument [16]. For test retest reliability, the average diary scale score from week two of the placebo run-in period was compared to week three of the placebo run-in period for all patients. The 95% CLs were calculated using the Jackknife method [14].

Longitudinal construct validity was evaluated with Pearson's correlation coefficients (PCC), to determine the relationship between changes in the daytime and nocturnal asthma symptom scales and other measures of airway function over a period of time. The relationship between the change in average diary scale scores and FEV₁, PEF, and β -agonist inhaler use from the end of the placebo run-in period to the end of the treatment period were examined. *A priori*, we expected to see higher correlations between the diary scale scores and other asthma measures that are also reported on a daily basis (such as peak expiratory flow) than with those measures collected periodically (such as FEV₁). For these analyses, morning and evening PEF measures were averaged for the week as a daily PEF. PEF measurements that were performed after the use of β -agonist inhaler were combined with those made without prior β -agonist use both in the placebo run-in and treatment periods, although patients were instructed to abstain from use of their β -agonist inhaler prior to PEF measurement.

Responsiveness is the extent to which the diary scale score changes when subjects improve or deteriorate. A trend test [17] across placebo and four active treatment dose groups was applied to the change in the diary symptom scale scores (from the last 2 weeks of the placebo run-in period to the last 2 weeks of the treatment period) to assess responsiveness.

Results

A total of 346 patients were enrolled into two clinical studies. Two hundred and thirty nine patients were randomized into clinical trial A (44 into the placebo group and 49, 48, 49 and 49 into the four dose groups of active treatment). One hundred and seven were randomized into clinical trial B (53 into placebo and 54 into active treatment groups). Thirteen patients were discontinued prior to completing the studies. Therefore, complete data on 333 patients are available for this report (229 and 104 for clinical trials A and B, respectively). The baseline characteristics for all patients entered, by study, are reported in table 1. In clinical trial A, 87% (209 of 239) of the patients reported awakenings with asthma symptoms, and in clinical trial B 76% (81 of 107) reported awakenings. Awakenings were defined as having at least two awakenings (at night or

Table 1. – Baseline characteristics of asthma patients in clinical trials A and B

Characteristics	Clinical trial A (n=239)	Clinical trial B (n=107)
Age yrs	35 (18–68)	44 (19–65)
Males n (%)	141 (59)	72 (67)
FEV ₁ L·s ⁻¹	2.48±0.71 (0.9–3.9)	2.29±0.70 (1.1–4.0)
Daily β -agonist use puffs·day ⁻¹	5.6±3.3 (0.2–19.0)	6.0±3.9 (0–23.2)
PEF L·min ⁻¹	418.6±97.0 (153.4–678.9)	398.8±96.1 (237.5–673.0)
Baseline daytime scale score	2.25±0.78 (0–6)	2.49±0.67 (0–6)
Baseline nocturnal scale score	1.08±0.86 (0–3)	0.71±0.82 (0–3)
Awakenings question n (%)	209 (87)	81 (76)

Values are presented as mean±SD, and range in parenthesis unless otherwise indicated. FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow.

in the morning) with asthma symptoms in a 1 week period of time during the placebo run-in period.

The internal consistency and test retest reliability for the daytime scale and the test retest reliability for the nocturnal scale are presented in table 2. Internal consistency for the nocturnal scale is not applicable, since this scale consists of only one question.

The daytime scale showed a high level of internal consistency (Cronbach's alpha = 0.92 and 0.90 in studies A and B, respectively) and acceptable reliability (ICC = 0.69 and 0.74 in studies A and B, respectively). The nocturnal diary scale showed stronger reliability in both studies (ICC = 0.83 and 0.87, respectively).

In general, the longitudinal construct validity correlations were moderate-to-strong and in the expected direction between change in symptoms on the asthma symptom scales and change in FEV₁, PEF and puffs of β -agonist inhaler use (table 3); *i.e.* as the average change in symptom scale score decreased (improved), the average change in FEV₁ and PEF increased (improved) and puffs of inhaler decreased (improved). Correlations were strongest between the symptom scale scores and puffs of β -agonist inhaler used, and weakest between the symptom scale scores and FEV₁, which was measured weekly at clinic visits.

Table 2. – Internal consistency and test retest reliability

Diary type	Clinical trial A (n=229)	Clinical trial B (n=104)
Daytime scale	0.92 (0.89–0.94)	0.90 (0.83–0.94)
Cronbach's alpha		
Daytime scale	0.69 (0.56–0.79)	0.74 (0.56–0.85)
ICC		
Awakenings scale	0.83 (0.78–0.89)	0.87 (0.77–0.93)
ICC		

Values in parentheses are 95% confidence limits calculated with Jackknife procedure [17]. ICC: intraclass correlation coefficient.

Table 3. – Longitudinal construct validity (correlations between change in diary scores and change in other asthma measures from baseline)

Diary type	Pearson correlation coefficients (95% confidence interval)*					
	Clinical trial A (n=229)			Clinical trial B (n=104)		
	FEV1	PEF	β-agonist inhaler puffs	FEV1	PEF	β-agonist inhaler puffs
Daytime scale	-0.28 (-0.39 to -0.16)	-0.49 (-0.58 to -0.38)	0.64 (0.56 to 0.71)	-0.25 (-0.42 to -0.06)	-0.38 (-0.53 to -0.20)	0.58 (-0.43 to 0.69)
Awakenings scale	-0.38 (-0.48 to -0.26)	-0.32 (-0.43 to -0.20)	0.48 (0.37 to 0.57)	-0.28 (-0.45 to -0.09)	-0.51 (-0.64 to -0.35)	0.47 (0.30 to 0.61)

*: Pearson correlation coefficients are significant. For definitions see legend to table 1.

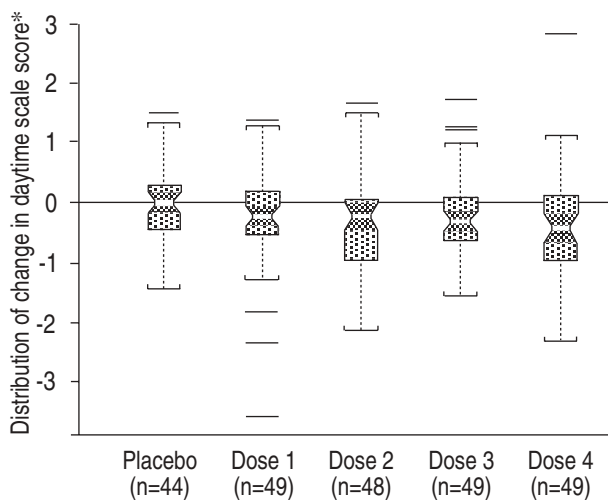


Fig. 1. – Responsiveness of daytime diary scale (change from baseline in daytime symptom diary scale over placebo and four drug dose groups). The graph is a standard box and whisker plot, providing median, 25th and 75th percentile and 1.5 × interquartile range (whiskers). Points outside the whiskers are shown as horizontal bars. *: change in score from last 2 weeks of placebo run-in period to the last 2 weeks of active treatment or placebo treatment in clinical trial A.

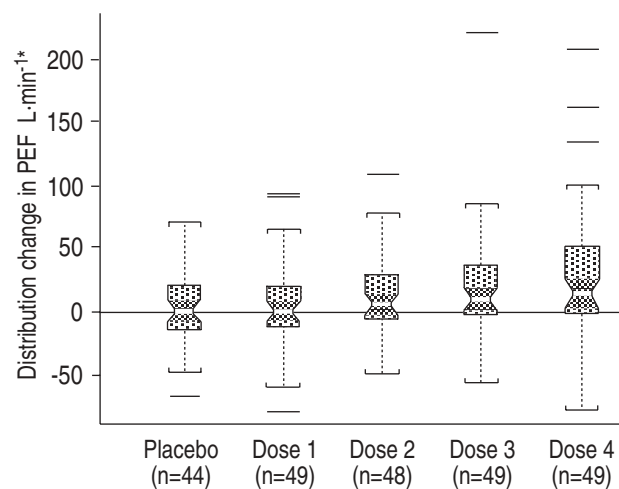


Fig. 2. – Dose response for peak expiratory flow (PEF) (change from baseline in peak expiratory flow over placebo and four drug dose groups). The graph is a standard box and whisker plot, providing median, 25th and 75th percentile and 1.5 × interquartile range (whiskers). Points outside the whiskers are shown as horizontal bars. *: change in score from last 2 weeks of placebo run-in period to the last 2 weeks of active treatment or placebo treatment in clinical trial A.

Figure 1 graphically represents the responsiveness of the daytime symptom scale to treatment, by presenting the distribution of change in the diary score across drug treatment dose groups. The daytime and nocturnal diary scales responded to drug treatment in the expected direction; specifically, as the drug dose increased, greater improvements were observed in symptoms.

The daytime scale was found to be responsive to change across the drug dose groups in clinical trial A (p-value for trend test =0.048). However, the difference between treatment and placebo in clinical trial B was not significant (p=0.103). In a similar manner to the daytime scale, the nocturnal scale detected a response across the dose groups for clinical trial A (p=0.025), but not for clinical trial B (p=0.101). In concordance with the results presented for the asthma symptom scales, the average change in the asthma measures of FEV1, PEF and β-agonist inhaler use showed greater improvements in the drug-treated groups as compared to the placebo-treated group. Figure 2 displays the distribution of change in PEF over drug dose groups, which is fairly similar to the distribution of change across drug treatment doses seen for the daytime symptom scale (fig. 1).

Discussion

The daytime and nocturnal asthma symptom diary scales were shown to have acceptable reliability, longitudinal construct validity and responsiveness, using the scoring methodology specified in the methods section. Additionally, the daytime scale was found to have good internal consistency. The diary scales were employed in clinical studies where patients concurrently recorded PEF and β-agonist inhaler use. Therefore, the reliability, validity and responsiveness of the diary symptom scales, as described in this report, are dependent on concurrent measurement with these more objective measures of asthma burden.

There have been few studies published validating asthma symptom scales. GIBSON *et al.* [9] validated a daily asthma symptom diary and a weekly asthma symptom questionnaire evaluating cough, chest tightness, breathlessness and wheeze in an open-label, non-controlled study using inhaled corticosteroid withdrawal. MALO *et al.* [6] examined the ability of a simple daily diary (records nocturnal asthma, symptoms on awakening and absence from school or work) to document asthma exacerbations

in a single-blind, randomized study. A monthly assessment of asthma was evaluated by STEEN *et al.* [10], using an observational study without manipulation of asthma therapy. We validated our daytime and nocturnal diary scales in two randomized, double-blind, placebo-controlled asthma trials.

In the absence of a gold standard, the validity of a questionnaire assessing a disease state may be determined by examining the correlations between the questionnaire and other clinical measures related to the disease. In this way, JUNIPER and co-workers [2] and others [6–9] have correlated subjective measures of asthma, such as asthma symptom questionnaires or asthma-specific quality of life domains, with more objective measures of asthma, such as FEV₁, PEF and β -agonist inhaler use. Consistent with other research in adult asthmatics, we found that changes in our asthma symptom scale scores were significantly correlated with changes in FEV₁, PEF, and β -agonist inhaler use [6–9]. It is not unexpected that the correlation coefficients between change in symptoms and change in pulmonary function, whilst significant, are only moderately correlated (coefficients = -0.25 to -0.51), since symptoms and pulmonary function appear to be measuring different clinical aspects of asthma [18].

We found a stronger relationship between change in patient-reported asthma symptoms and changes in PEF and β -agonist inhaler use than with change in FEV₁ levels. This stronger relationship may be due to patients responding to the symptom diary scale questions based on their PEF level or β -agonist inhaler use for that day [19]. However, JUNIPER and co-workers [2] also found higher correlation coefficients between change in domains of the asthma-specific quality of life questionnaire (which includes asthma symptom and activities domains) and change in patient reported measures, such as PEF and medication use, than with change in FEV₁, even though both the asthma-specific quality of life questionnaire and FEV₁ were completed periodically (weeks 0, 4 and 8 of their study), and the PEF and medication use were recorded daily on a diary.

A limitation of our PEF data collection method was that we were unable to separate the PEF measurements into pre- and post-agonist inhaler use. Given that β -agonist inhaler use decreased during the study, one might expect that the use of β -agonist prior to PEF measurement might also have decreased. A decrease in use of β -agonist inhaler prior to PEF could result in a paradoxical drop in PEF during the study period. If PEF declined in some patients while symptoms and β -agonist use improved, the strength of the relationship between symptoms and PEF may be greater than that observed. On the other hand, if β -agonist inhaler use prior to PEF measurement increased during the study, both symptom scores and PEF would be expected to improve (since these measurements were recorded at the same time), and the correlation would be similar to or smaller than that found.

The daytime and nocturnal symptom scales were responsive to drug therapy in clinical trial A. Lack of a statistically significant response of the diary scales in clinical trial B may be due to its smaller sample size, since a trend in the expected direction (although not significant) was observed. Alternatively, the diary scales may be less than optimally responsive. Examination of the pulmonary function measures in the two trials showed that,

while peak flow was significantly responsive in both trials, FEV₁ was only responsive in clinical trial B. The two clinical trials tested an investigational drug for asthma against placebo. While this drug appeared to have antiasthma activity, the effects on FEV₁ were generally modest [20]. Consequently, the response of the diary symptom scales to drug *versus* placebo in these trials and the lack of a significant response for FEV₁ in trial A may be more a reflection of the drug's relative efficacy.

Based on the observed measurement characteristics of the asthma symptom diary scales reported here, we believe these diaries have been adequately validated and are appropriate for inclusion in clinical trials of asthma therapy. We recommend that an evaluation of asthma in clinical trials include objective pulmonary measures, such as forced expiratory volume in one second or peak expiratory flow, assessment of change in need for acute bronchodilator medication and assessment of asthma symptoms and their effects on activities, with either a validated diary or periodic questionnaire to fully understand the impact of asthma therapy. Additional studies are being conducted, which will evaluate how well the diary scales respond in asthma patient populations with differing asthma severity and those treated with other noninvestigational asthma therapies.

Appendix*

Daytime symptom diary scale questions

1) How often did you experience asthma symptoms today?

0	1	2	3	4	5	6
None of the time						All of the time

2) How much did your asthma symptoms bother you today?

0	1	2	3	4	5	6
Not at all bothered						Severely bothered

3) How much activity could you do today?

0	1	2	3	4	5	6
More than usual activity						Less than usual activity

4) How often did your asthma affect your activities today?

0	1	2	3	4	5	6
None of the time						All of the time

Nocturnal diary scale question

1) Did you wake up with asthma symptoms. (This can be awakening in the middle of the night or on awakening in the morning)?

No Once More than once Awake "all night"

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