Predicting Asthma Treatment Outcome at Diagnosis: The Role of Symptom Perception during a Histamine Challenge Test

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Objective. In asthma, many treatment decisions are dependent upon patient perception/patient report of asthma symptoms. Discrepancies between patient perception of asthma symptoms and objective indicators of pathophysiology are widespread and can hinder asthma treatment. Early detection of problems in asthma symptom perception may be a first step to help these patients. We investigated the predictive value of symptom perception during a histamine challenge test (HCT) at asthma diagnosis for patient-rated outcome of asthma treatment 3 months later. Methods. In a prospective observational study, persons with asthma (N = 60) showing bronchial hyperresponsiveness in a HCT completed questions on asthma symptoms and negative affectivity (NA). The HCT was extended with an ambiguous situation suggesting asthma symptoms despite physiological recovery. Lung function (forced expiratory volume in 1 second (FEV1)) and symptom ratings were measured during the test (after each histamine dosage), and we constructed several measures of asthma symptom perception based on FEV1 and symptom ratings. Three months later, 30 participants completed questionnaires on asthma control and asthma-related quality of life. Results. Symptoms reported during HCT predicted worse asthma control and quality of life 3 months later. The prospective association between symptoms during HCT and asthma control remained significant when controlling for NA and baseline lung function. These effects were strongest for symptoms during ambiguous situations. Conclusions. Higher symptom levels at the start of the HCT and during recovery may reflect a tendency to inaccurately perceive asthma symptoms in ambiguous situations. Assessing symptoms during diagnostic challenge tests can help predict problems with asthma treatment.

Keywords asthma, asthma control, histamine challenge test, patient-reported outcome, quality of life, symptom perception

INTRODUCTION

Asthma treatment guidelines focus on obtaining optimal asthma control (1), yet real-world asthma control still remains surprisingly low, with 50–70% of patients not achieving optimal asthma control (2–4). In this study, we explored the prospective relationship between inaccurate perception and asthma control.

A discrepancy between self-reported symptoms and objective indicators of pathophysiology has a high prevalence in asthma (5). Challenge test procedures such as histamine and metacholine challenge tests can be used not only to assess bronchial hyperresponsiveness (BHR) (6) but also to provide an opportunity to assess the perception of respiratory symptoms in a clinical context. Using these tests, differences in asthma symptom perception have been related to asthma severity (7–9), inhaled corticosteroid use (10, 11), daily-life symptom levels (9), anxiety and negative affectivity (NA) (7, 12–14), and catastrophic thinking about asthma (12).

Methods to assess symptom perception during challenge tests differ across studies, which may explain inconsistent findings. For instance, anxiety has been found to increase sensitivity to airway change, increase symptoms regardless of lung function, or not have an effect on symptom perception (7, 12, 15, 16).

Our model of asthma symptom perception (5), which specifies the role of cognitive and affective variables in asthma symptom perception, may help us to understand these inconsistent findings. According to this model, asthma symptom perception is influenced not only by emotions and expectations but also by person variables such as NA and mental models of previous asthma episodes and symptoms. The model further specifies that these aforementioned effects will have a greater influence on symptom reports when sensory information is ambiguous and not when sensory information is intense. This is in line with the general finding that ambiguity enhances the influence of interindividual differences (17).

The latter specification has important implications for the use of the histamine challenge test (HCT) as a source of relevant information for symptom perception and asthma control. The test starts out relatively ambiguous: a person may expect to perceive symptoms, but the sensory information may be relatively weak due to the initial low dosages of histamine. As the challenge test continues and bronchoconstriction increases, more intense sensory information becomes available. The varying degree of ambiguity during the test may explain the inconsistent effects of anxiety on symptom perception that have been found previously. Furthermore, familiarity with the HCT procedure may alter ambiguity. Participants may learn to associate the beginning of the test with the absence of symptoms and the end of the test with high levels of asthma symptoms (18). In this study, we therefore investigated symptom perception...
perception during the HCT in persons who did not have previous experience with the test. To further increase the variation in ambiguity during the HCT, we included a situation at the end of the test wherein contextual information suggested a state of asthma symptoms despite physiological recovery. This ambiguous situation can be seen as an approximation of ambiguous symptom situations in daily life and may therefore be especially relevant to tap interindividual differences in symptom perception.

In addition, we measured the intensity and unpleasantness of asthma symptoms on separate scales to explore potential differences between these two components of the symptom experience.

In this study, our aim was to investigate the prospective relationship between symptom perception and asthma outcome. So far, most studies relating symptom perception to clinical outcome have been cross-sectional. Exceptions are a study by Bijl-Hofland et al. (9), which found a relationship between symptom perception during the HCT and symptoms in daily life in the 3-month period preceding the HCT, and a study by Martínez-Moragón et al. (19), which found that stability in overperception of asthma symptoms in histamine challenges 9 years apart is related to higher anxiety levels.

In our study, we expected that interindividual differences during ambiguous sensory stimulation would be more predictive of asthma control and asthma-related quality of life 3 months later than during intense sensory stimulation.

**METHODS**

**Participants**

Participants were recruited from a group of 110 consecutive clinic outpatients who underwent histamine challenge testing for the first time, as part of a protocol for asthma diagnosis. BHR was defined as a decrease in forced expiratory volume in 1 second (FEV$_1$) during the HCT of at least 20% compared with baseline FEV$_1$. Asthma diagnosis was based on guidelines from the Global Initiative for Asthma (GINA) (1). Reasons for non-inclusion were no BHR or asthma diagnosis (34 patients), baseline FEV$_1$ <50% of the predicted value (5 patients), technical problems (6 patients), or language barriers (5 patients). Sixty patients (26 female) with asthma and BHR participated in the study. Asthma severity ratings were retrieved from clinic records and were based on GINA guidelines (1). Asthma severity was distributed as follows: 16 patients had intermittent asthma, 7 had mild persistent asthma, and 23 had moderate persistent asthma. For 14 patients, clinic records did not include the necessary information to assess asthma severity. Thirty patients (16 female) participated in the follow-up study. Participants did not receive any compensation for participation.

**Self-Report Measures**

Asthma control was measured using the Asthma Control Test (ACT) (20). The ACT includes questions on shortness of breath, nocturnal symptoms, rescue inhaler use, impact of asthma on work/school, and patient-rated control. Each question is scored on a scale ranging from 1 to 5. A cutoff sum score $\geq$20 indicates good asthma control.

Limitations in asthma-related quality of life were measured using the Asthma Quality of Life Questionnaire (AQLQ) (21, 22). The questionnaire consists of four domains: symptoms, emotions, exposure to environmental stimuli, and activity limitations. Participants score each item on a scale ranging from 1 (low quality of life) to 7 (high quality of life).

Trait NA was measured using the NA scale of the Positive and Negative Affect Schedule (PANAS) (23, 24). Participants rated to which degree 10 negative adjectives were applicable to themselves on a scale ranging from 1 (very little or not at all) to 5 (very much).

Perceived asthma symptoms were measured using the Asthma Symptom Checklist (ASC) (25), a 36-item checklist consisting of six subscales (obstruction, dyspnea, hyperventilation symptoms, fatigue, anxiety, and irritable). Patients rated their current symptom intensity on an 11-point scale ranging from 0 (not at all) to 10 (symptoms as bad as possible).

During the HCT, we measured intensity and unpleasantness of asthma symptoms using 100 mm visual analog scales (VASs). The intensity scale (VAS-I) was anchored at 0 (not noticeable) and 100 (maximal intensity imaginable). The unpleasantness scale (VAS-U) was anchored at 0 (not unpleasant) and 100 (maximal unpleasantness imaginable). VASs have been used previously to measure intensity and unpleasantness of asthma symptoms (e.g., (26)).

**Modified Histamine Challenge Test**

The modified HCT was based on the protocol by Cockcroft et al. (6). On the day of the study, patients had not taken any short-acting $\beta_2$-agonists and anticholinergics for 8 h, long-acting $\beta_2$-agonists and theophyllines for 24 h, and antihistamines and long-acting anticholinergics for 48 h. Inhaled corticosteroids were allowed. After baseline spirometry, participants inhaled a series of aerosols, starting with a solution of 0.09% NaCl (baseline inhalation), followed by doubling dosages of histamine (0.25–8 mg/ml, in a solution of 0.09% NaCl). The aerosols were generated using compressed air with a flow of 6 l/min via a System 22 Disposable Sidestream Nebulizer (Medic-Aid, Pagham, UK; mass median diameter 3 µm, respirable output 80%). Patients inhaled the aerosols for 2 min with 5 min intervals between dosages. After each 2 min inhalation, spirometry was performed according to guidelines of the European Respiratory Society (27). After spirometry, participants rated the intensity and unpleasantness of their current asthma symptoms using the VAS scales. The increase in histamine dosage continued until a 20% drop in FEV$_1$ occurred or until after the inhalation of 8 mg/ml histamine. The provocative concentration leading to a 20% drop in FEV$_1$ (PC$_{20}$) was determined by linear interpolation from the last two points on the log dose–response curve.
The modification of the HCT consisted of administering nebulized salbutamol in a final inhalation trial as if it were the next histamine challenge trial. We used 1 ml of nebulizer solution (Ventolin®, 5 mg/ml nebulizer solution, GlaxoSmithKline, Brentford, UK), diluted with 2 ml of a solution of 0.09% of NaCl to guarantee maximal reversion of the bronchoconstriction. Because the administration of salbutamol appeared similar to a regular histamine trial, and participants were not informed that salbutamol would be administered in nebulized form, this created an ambiguous situation wherein contextual information predicted sustained or worsening asthma symptoms, despite a recovery of bronchoconstriction. Twenty minutes after salbutamol inhalation, spirometry was performed, and participants again rated intensity and unpleasantness of their asthma symptoms. Thereafter, participants were given two puffs from a placebo metered-dose inhaler (propellant only, Allen & Hanburys, Uxbridge, UK) to suggest symptom relief and to make the procedure as similar as possible to the regular HCT.

Procedure

The study was approved by the ethical review board of the University Hospital Gasthuisberg, Leuven, Belgium (study number S51019). First, participants received oral and written information about participation. They were informed that, as part of their diagnostic protocol, they would inhale increasing dosages of histamine. This histamine inhalation could lead to an increase in asthma symptoms, but would stop when a 20% decrease in lung function was observed. Afterward they were to receive metered-dose inhaler medication to counteract the effect of histamine inhalation. After providing informed consent, participants filled out questionnaires (PANAS, ASC) in the waiting room. Baseline spirometry was performed and was followed by the modified HCT. Afterward, participants were debriefed and reminded of the follow-up procedure. Follow-up questionnaires (ACT, AQLQ, ASC) were mailed to participants 3 months after the HCT, accompanied by a cover letter and a postage-paid return envelope. Both e-mail and phone reminders were used to improve follow-up participation.

Data Reduction and Data Analysis

We explored differences between male and female participants and between participants dropping out or participating in follow-up using Student t-tests. To study the predictive value of the HCT for treatment outcome, we assessed asthma symptom perception using three indices that take into account both asthma symptoms and lung function. For each participant, we regressed VAS symptom levels on changes in FEV1 (12, 28). This led to a slope variable (slope ΔFEV1), indicating the sensitivity to perceive changes in bronchoconstriction, and an intercept variable (intercept ΔFEV1), indicating the baseline symptom level. Perception score for a 20% reduction in FEV1 (PS20) (29) was determined by extrapolation from the last two histamine inhalations. Four participants (two of them participating in the follow-up questionnaires) showed a drop in FEV1 >20% baseline after the first histamine inhalation. For these participants, 0.25 was used as an approximation of their PC20 and symptom ratings after histamine inhalation were used as an approximation of PS20.

Apart from these symptom perception indices, we also included raw VAS symptom ratings from the HCT trials. We chose only to include VAS ratings at baseline, after saline inhalation, after the final histamine inhalation (final H), and 20 minutes after salbutamol inhalation (S20), resulting in situations with varying ambiguity. For each of these situations, we had corresponding lung function measurements for all participants (the format of the HCT resulted in an unequal number of histamine trials across participants).

There were some missing data in the available follow-up questionnaires (3%). We remediated this problem using multiple imputation for missing data (using the SAS proc mi procedure). To analyze the follow-up data, we correlated information gathered during baseline and histamine challenge (symptom perception indices, NA, physiological indices, VAS symptom data) with outcome variables (ACT, AQLQ, ASC) using Pearson correlations. We used general linear models to investigate the predictive effect of symptom perception above the effect of NA, baseline FEV1, and PC20. All analyses were performed using SAS 9.1.3 software (SAS Institute Inc., Cary, NC).

RESULTS

Sample Characteristics

Clinical characteristics and questionnaire data at baseline and asthma symptom perception indices are displayed in Table 1. Observed symptoms during HCT are displayed in Figure 1. Follow-up data are displayed in Table 2.

Compared with men, women had higher baseline ASC symptoms (t(df = 58) = 2.11; p = .04) and higher ΔFEV1 intercept indices (intensity t(df = 58) = 3.16; p < .01; unpleasantness t(df = 58) = 3.04; p < .01). Differences in ΔFEV1 slope indices neared statistical significance (intensity t(df = 58) = −1.93; p = .06; unpleasantness t(df = 58) = −1.83; p = .07). Furthermore, men and women differed in their perception of asthma symptoms during the HCT, with women reporting more asthma symptoms (baseline, saline; Figure 1). Interestingly, this gender difference disappeared for symptoms at the end of the HCT (intensity final H t(df = 58) = 1.05; p = .30; unpleasantness final H t(df = 58) = 1.32; p = .19) and reappeared after salbutamol inhalation (S20; Figure 1). There were no significant differences between women and men on any of the follow-up data (Table 2).

Compared with patients who did participate in the follow-up study, patients who did not participate had lower symptoms at S20 intensity t(df = 58) = −2.32; p = .02; unpleasantness t(df = 58) = −2.21; p = .03) and steeper slope coefficients (intensity t(df = 58) = 3.18; p < .01; unpleasantness t(df = 58) = 3.01; p < .01), which may signify lower symptom accuracy in patients who
participated in the follow-up study. Differences between the two groups on all other variables were not significant.

**Predictors of Asthma Outcome**

Pearson correlations of baseline and HCT variables with the different patient-rated outcome variables are listed in Table 3. Baseline FEV₁ and PC₂₀ did not predict asthma control or quality of life, whereas NA and baseline ASC did. The slope indices and PS₂₀ did not predict patient-rated asthma outcome 3 months later. However, intercept indices did predict patient-rated asthma control and quality of life.

Physiological response to salbutamol did not predict patient-rated outcome (all p values >.45). VAS symptom ratings were correlated with asthma control and quality of life (Figure 2a and b). Overall, VAS ratings of the unpleasantness of asthma symptoms were better predictors of asthma control and quality of life than ratings of histamine symptom intensity. VAS ratings during ambiguous situations (Saline, S₂₀) were better predictors of asthma control than symptom ratings during less ambiguous situations (baseline, final H), with the relationship between final H and asthma control not reaching statistical significance. Only the level of asthma symptoms at S₂₀ was a significant predictor of asthma-related quality of life.

When controlling for gender, NA, PC₂₀, and baseline FEV₁, the association between VAS ratings and ACT scores remained significant (Figure 2c), unlike the association between asthma symptoms and AQLQ scores.

**DISCUSSION**

We studied symptom perception during a modified HCT as part of the protocol for asthma diagnosis and its relationship with asthma outcome. Our results show that higher levels of NA and higher symptom levels at baseline and during the HCT predicted poorer asthma control and lower quality of life 3 months later, whereas physiological measures (baseline FEV₁, PC₂₀, and FEV₁ response to salbutamol) were not related to the outcome of asthma treatment. More specifically, asthma symptoms during the ambiguous situations of the HCT (saline, 20 min after salbutamol inhalation) were better predictors of outcome than symptoms during the least ambiguous situation (final histamine inhalation). For the asthma symptom perception indices, the results were similar: the intercept of the relationship between ΔFEV₁ and asthma symptoms predicted

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**TABLE 1.**—Sample characteristics at baseline.

| Characteristic | Total (n = 60) | Female (n = 26) | Male (n = 34) |
|---------------|---------------|----------------|--------------|
| Age           | 36.38 ± 16.41 | 35.46 ± 16.90  | 37.09 ± 16.25 |
| Baseline FEV₁ | 102.73 ± 14.62| 104.58 ± 11.39 | 101.32 ± 16.71 |
| NA            | 19.87 ± 5.65  | 20.00 ± 5.73   | 19.76 ± 5.67  |
| ASC-Now       | 1.18 ± 1.36   | 1.60 ± 1.52    | 0.87 ± 1.15   |
| PC₂₀          | 2.23 ± 1.83   | 2.02 ± 1.46    | 2.39 ± 2.08   |

Indices intensity of asthma symptoms

| PS₂₀          | 47.18 ± 22.66 | 49.92 ± 22.73 | 45.09 ± 22.72 |
| Slope ΔFEV₁   | 1.20 ± 0.80   | 0.98 ± 0.57   | 1.37 ± 0.91   |
| Intercept ΔFEV₁ | 21.36 ± 19.04| 29.64 ± 20.88| 15.03 ± 14.92**|

Indices unpleasantness of asthma symptoms

| PS₂₀          | 48.88 ± 25.38 | 52.43 ± 25.14 | 46.16 ± 25.61 |
| Slope ΔFEV₁   | 1.23 ± 0.90   | 0.99 ± 0.66   | 1.42 ± 1.02   |
| Intercept ΔFEV₁ | 22.27 ± 21.03 | 31.11 ± 23.20 | 15.51 ± 16.56**|

Notes: FEV₁, forced expiratory volume in 1 second; NA, negative affectivity; ASC-Now, current symptom intensity measured by the Asthma Symptom Checklist; PC₂₀, provocative concentration of histamine leading to a 20% reduction in FEV₁; PS₂₀, perception score for a 20% reduction in FEV₁; slope ΔFEV₁, slope of the analysis regressing symptom levels on changes in FEV₁; intercept ΔFEV₁, intercept of the analysis regressing symptom levels on changes in FEV₁.
P-values:

*p < .05, **p < .01.

**TABLE 2.**—Follow-up sample characteristics.

| Characteristic      | Total (n = 30) | Female (n = 16) | Male (n = 14) |
|---------------------|---------------|----------------|--------------|
| Asthma control (ACT)| 20.82 ± 4.01  | 20.85 ± 3.89   | 20.79 ± 4.30 |
| Quality of life (AQLQ) | 5.68 ± 1.00  | 5.47 ± 0.99   | 5.93 ± 0.99  |

Note: ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire.

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**FIGURE 1.**—Differences between female and male participants on ratings of the intensity and unpleasantness of asthma symptoms during the histamine challenge test.
TABLE 3.—Pearson correlations between baseline characteristics and symptom perception indices with asthma control and quality of life 3 months later (n = 30).

| Variable                        | Asthma control | Quality of life |
|---------------------------------|----------------|-----------------|
| Age                             | −0.11          | −0.20           |
| Negative affectivity            | −0.42*         | −0.55**         |
| Baseline ASC                    | −0.69**        | −0.60**         |
| Baseline FEV₁                   | 0.04           | −0.06           |
| PC₂₀                            | 0.16           | 0.20            |
| Intensity histamine challenge test indices |                  |                 |
| Slope ΔFEV₁                     | −0.22          | −0.10           |
| Intercept ΔFEV₁                 | −0.54**        | −0.41*          |
| PS₂₀                            | −0.27          | −0.24           |
| Unpleasantness histamine challenge test indices |                  |                 |
| Slope ΔFEV₁                     | −0.21          | −0.12           |
| Intercept ΔFEV₁                 | −0.59**        | −0.44*          |
| PS₂₀                            | −0.35          | −0.28           |

Notes: ASC, Asthma Symptom Checklist; FEV₁, forced expiratory volume in 1 s; PC₂₀, provocative concentration of histamine leading to a 20% reduction in FEV₁; PS₂₀, perception score for a 20% reduction in FEV₁; slope ΔFEV₁, slope of the analysis regressing symptom levels on changes in FEV₁; intercept ΔFEV₁, intercept of the analysis regressing symptom levels on changes in FEV₁.

* p < .05, ** p < .01.

These results are in line with our prediction that perceived symptoms during the HCT are a better predictor of patient-rated outcome than perceived symptoms in unambiguous situations. In ambiguous situations, perception of symptoms may be more influenced by a person’s mental model of asthma symptoms than by sensory information (5, 17, 30, 31). In a person with asthma, real-life asthma situations are often characterized by a mixture of respiratory sensations of varying intensity, combined with person-specific and context-specific expectations (5). Therefore, the ambiguity caused by the modified HCT is an ideal laboratory analog for these ambiguous real-life situations. The high correlations between VAS ratings during ambiguous situations of the HCT and asthma control 3 months later suggest that variability in symptom perception during ambiguous situations in real life may contribute to the difficulty of achieving optimal asthma control in clinical practice.

A somewhat puzzling observation is the high predictive value of baseline symptoms in predicting patient-rated asthma outcomes. Both VAS ratings and ASC scores assessed at baseline (just before the start of the HCT) are good predictors of asthma control and asthma-related quality of life. In hindsight, assessing baseline symptoms may already constitute an ambiguous context. The HCT is announced, described, and administered in a hospital context, which may activate a symptom mindset (32). Furthermore, the novel situation may trigger arousal, which may add to the ambiguity at the beginning of the test. To accurately assess the influence of ambiguous contexts on the perception of asthma symptoms, it may be necessary to provide patients with a clear, unambiguous non-symptom situation.

Our findings are important for the treatment of patients with asthma. Patients who report more asthma symptoms during the ambiguous phases of the HCT may be prone to do so in ambiguous situations in daily life as well. This may lead to an increase of symptoms, a higher use of rescue medications, and an overall impairment of quality of life and asthma control, as is seen in the patient-reported outcomes in our study.

Using the HCT to detect inaccurate perception of asthma symptoms may inform health-care professionals of potential problems with asthma-related quality of life and asthma control during the course of asthma treatment and may indicate which persons may benefit from additional interventions focusing on symptom perception (see also (8, 29)). Furthermore, our study shows that the ambiguous start and recovery periods of the modified HCT are especially suited to discover meaningful differences in symptom perception. Patients are usually referred for HCT when corroborating evidence is needed in order to make an asthma diagnosis. It is possible that this subpopulation is especially vulnerable to inaccurate perception of asthma symptoms compared with patients with more severe levels of asthma who show less ambiguous asthma symptoms and are not referred for challenge testing. In order to convincingly implement this test in clinical practice, further studies are needed to assess symptom responses in a sample of participants showing a larger variation in asthma severity and to determine which indices and cutoff scores may be appropriate to predict whether a patient with asthma may benefit from an intervention focused on symptom perception.

The current study has a number of shortcomings that limit the scope of our findings. First, because of the relatively small number of participants, some statistical tests may have lacked power. Second, the high attrition rate in the follow-up group reduces the reliability of follow-up data. Differences in baseline characteristics of these groups furthermore suggest that dropout was not random, with patients in the dropout group exhibiting on average less problematic perception of asthma symptoms. Larger scale studies can be informative about smaller effects and can inform us if the results we found will hold up in a larger population. Third, the interval between the HCT and follow-up was only 3 months. Because of the chronicity of asthma and asthma treatment, it would be interesting to study whether problematic perception of asthma symptoms has predictive effects on a longer term. Fourth, asthma control at follow-up was measured only by self-report. Although the ACT shows good validity when compared with physician-rated control, inclusion of physician-rated asthma control or lung function measures may strengthen claims of a prospective association between symptom perception during a HCT and asthma control. Furthermore, we did not assess patient expectations of asthma treatment or self-efficacy, which may also interact with perception of asthma symptoms and treatment outcome (33). A further limitation is that we
did not measure expectancy of symptoms, nor mental models of asthma directly, so we cannot be certain that the effect of ambiguity during the HCT occurred because of expectancy and illness beliefs. The addition of multiple measurements during recovery or the inclusion of self-report data on symptom expectancy or affective state can remedy this shortcoming in further studies. Furthermore, persons with asthma differ in their specific asthma symptoms (e.g., shortness of breath, cough, wheezing, muscle fatigue) (25). A replication of this study with ASC symptom ratings after histamine challenge (cf. 18) may help us understand the relationship between the perception of specific asthma symptoms and their relationship with physiological measures and asthma outcome.

CONCLUSIONS
The results of the study show that symptom perception during the HCT is a predictor of patient-rated outcome of asthma treatment 3 months later. Supplementing the HCT with symptom ratings during the test may be a helpful
strategy to detect persons who will experience problems with asthma treatment and may be helped with additional interventions focusing on symptom perception.

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REFERENCES

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2010. Retrieved from www.ginasthma.org, December 2011.
2. Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-world Evaluation of Asthma Control and Treatment (REAT): findings from a national web-based survey. J Allergy Clin Immunol 2007; 119:1454–1461.
3. Gillissen A. Managing asthma in the real world. Int J Clin Pract 2004; 58:592–603.
4. Vandenplas O, Dramaix M, Joos G, Louis R, Michils A, Verleden G, Vincken W, Vints AM, Herbots E, Bachert C. The impact of concomitant rhinitis on asthma-related quality of life and asthma control. Allergy 2010; 65:1290–1297.
5. Janssens T, Verleden G, De Peuter S, Van Diest I, Van den Bergh O. Inaccurate perception of asthma symptoms: a cognitive-affective framework and implications for asthma treatment. Clin Psychol Rev 2009; 28:211–219.
6. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy 1977; 7:235–243.
7. Chen E, Hermann C, Rodgers D, Oliver-Welker T, Strunk RC. Symptom perception in childhood asthma: the role of anxiety and asthma severity. Health Psychol 2006; 25:389–395.
8. Bijl-Hofland ID, Cloosterman SGM, Folgering HT, Akkermans RP, van Schayck CP. Relation of the perception of airflow obstruction to the severity of asthma. Thorax 1999; 54:15–19.
9. Bijl-Hofland ID, Folgering HT, van den Hoogen H, Cloosterman SG, van Weel C, Donkers JM, van Schayck CP. Perception of bronchocstriction in asthma patients measured during histamine challenge test. Eur Respir J 1999; 14:1049–1054.
10. Bijl-Hofland ID, Cloosterman SGM, Folgering HT, van den Elshout FJJ, van Weel C, van Schayck CP. Inhaled corticosteroids, combined with long-acting beta 2-agonists, improve the perception of bronchocstriction in asthma. Am J Respir Crit Care Med 2001; 164:764–769.
11. Salome CM, Reddel HK, Ware SI, Roberts AM, Jenkins CR, Marks GB, Woolcock AJ. Effect of budesonide on the perception of induced airway narrowing in subjects with asthma. Am J Respir Crit Care Med 2002; 165:15–21.
12. De Peuter S, Lemaigre V, Van Diest I, Verleden G, Demedts M, Van den Bergh O. Differentiation between the sensory and affective aspects of histamine-induced bronchocstriction in asthma. Respir Med 2007; 101:925–932.
13. Martínez-Moragón E, Perpiñá M, Belloch A, de Diego A, Martínez-Francés ME. Asthma patients’ perception of dyspnea during acute bronchocstriction. Arch Bronconeumol 2003; 39:67–73.
14. Spinhoven P, van Peski-Oosterbaan AS, Van der Does AJ, Willems LN, Stierk PJ. Association of anxiety with perception of histamine induced bronchoconstriction in patients with asthma. Thorax 1997; 52:149–152.
15. Boulot LP, Courroyer I, Deschesnes F, Leblanc P, Nouwen A. Perception of airflow obstruction and associated breathlessness in normal and asthmatic subjects: correlation with anxiety and bronchodilator needs. Thorax 1994; 49:965–970.
16. Spinhoven P, Ormel J, Sleegers PPA, Kempen GJM, Speckens AEM, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997; 27:363–370.
17. Lissek S, Pine DS, Grillon C. The strong situation: a potential impediment to studying the psychobiology and pharmacology of anxiety disorders. Biol Psychol 2006; 72:265–270.
18. De Peuter S, Put C, Lemaigre V, Demedts M, Verleden G, Van den Bergh O. Context-evoked overperception in asthma. Psychol Health Med 2007; 22:737–748.
19. Martínez-Moragón E, Perpiñá M, Belloch A, Serra B, Lloris A, Macián V. Evolution over time in over perceivers of dyspnea in asthma. Arch Bronconeumol 2006; 42:120–124.
20. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, Kosinski M, Pendergraft TB, Jhingran P. Asthma control test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006; 117:549–556.
21. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hillek TK. Evaluation of improvement of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992; 47:76–83.
22. Put C, Van den Bergh O, Lemaigre V, Demedts M, Verleden G. Evaluation of an individualised asthma programme directed at behavioural change. Eur Respir J 2003; 21:109–115.
23. Engelen U, De Peuter S, Victor A, Van Diest I, Van den Bergh O. Verdere validering van de “Positive and negative affect schedule” (PANAS) en vergelijking van twee nederlandstalige versies [Further validation of the Positive and Negative Affect Schedule (PANAS) and comparison of two Dutch versions]. Gedrag Gezond 2006; 34:89–102.
24. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988; 54:1063–1070.
25. Ritz T, Bobb C, Edwards M, Steptoe A. The structure of symptom report in asthma: a reevaluation. J Psychosom Res 2001; 51:639–645.