

Effects of Individual Self-Management Education on Clinical, Biological, and Adherence Outcomes in Asthma

Susan L. Janson, DNSc, John V. Fahy, MD, Jack K. Covington, Steven M. Paul, PhD,
Warren M. Gold, MD, Homer A. Boushey, MD

BACKGROUND: Asthma guidelines urge teaching patients the knowledge and skills required for self-management, based on the assumption that education will lead to improved skills and better asthma control.

METHODS: In a prospective, randomized controlled trial of 65 adults with mild-to-moderate asthma, we examined whether an educational self-management intervention would improve adherence to inhaled corticosteroid therapy, decrease markers of airway inflammation, and improve clinical control. Peak flow, symptoms, and adherence were monitored for 7 weeks. After a 1-week run-in, subjects were assigned randomly to either the educational intervention or control group. The 30-minute intervention was delivered and reinforced at biweekly intervals.

RESULTS: Compared with the control group, the intervention group had improvements in adherence to inhaled corticosteroid therapy (by 30% vs. -5%, $P = 0.01$), self-reported control of asthma (by 14% vs. 5%, $P = 0.04$), and perhaps quality of life (by 37% vs. 21%, $P = 0.06$). The direction of change for all other clinical outcomes was more favorable in the intervention group, but not significantly so. Markers of inflammation in sputum decreased more in the intervention group, with sputum eosinophils declining significantly ($P = 0.02$).

CONCLUSION: In asthmatic patients treated with inhaled corticosteroids, education and training in self-management improves adherence with inhaled therapy, perceived control of asthma, and sputum eosinophilia. *Am J Med.* 2003;115:620-626. ©2003 by Excerpta Medica Inc.

Asthma affects approximately 17 million people in the United States (1). Its treatment requires daily self-management, which in turn depends on the acquisition and mastery of specific knowledge and skills (2-6). Several elements of asthma education are thought to be essential for self-management, including the central role of airway inflammation, actions of anti-inflammatory and bronchoactive medications, correct inhalation technique, skills in monitoring and self-assessment, strategies for environmental control, and an action plan for asthma exacerbations (7). These key educational messages should be delivered in the context of providing medical care. The assumption underlying these recommendations is that imparting basic information and skills will lead to behavior that will improve asthma control. We examined this assumption by assessing the effects of individual self-management education on adherence to anti-inflammatory medication, biological markers of airway inflammation, and clinical outcomes.

From the Departments of Community Health Systems (SLJ, JKC) and Medicine (SLJ, JVF, WMG, HAB), Division of Pulmonary and Critical Care Medicine, and Office of Research (SMP), School of Nursing, University of California, San Francisco.

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Requests for reprints should be addressed to Susan L. Janson, DNSc, Department of Community Health Systems, University of California, San Francisco, Box 0608, San Francisco, California 94143-0608, or susanj@itsa.ucsf.edu.

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METHODS

Study Design

We conducted a prospective, randomized controlled trial of an individually delivered asthma educational self-management intervention in adults with mild-to-moderate asthma who were treated with an inhaled corticosteroid. We assessed adherence with inhaled corticosteroid medication using an electronic recording device (Doser; NewMed Corp., Newton, Massachusetts); the intensity of airway inflammation by measuring the constituents of induced sputum; and asthma control by measuring the frequency of "as needed" use of albuterol, symptom severity, pulmonary function, perceived asthma control, and asthma-related quality of life. The study was approved by the university institutional review board. All subjects provided written consent to participate.

Study Participants

Adults with mild-to-moderate persistent asthma (7) who had been prescribed an inhaled corticosteroid (dose $\geq 400 \mu\text{g/d}$) were recruited from clinics in the San Francisco Bay Area. Inclusion criteria were a history of physician-diagnosed asthma; age between 18 and 55 years; nonsmoking (lifetime smoking history ≤ 5 pack-years; none in the last year); and bronchial hyperresponsiveness to inhaled methacholine (concentration causing a 20% fall in forced expiratory volume in 1 second [FEV_1] of $< 8 \text{ mg/mL}$). Subjects with baseline $\text{FEV}_1 < 60\%$ predicted, $> 20\%$ variability, or fall in FEV_1 with diluent did not undergo methacholine challenge. Exclusion criteria in-

cluded treatment with oral corticosteroids within 4 weeks; upper respiratory tract infection within 6 weeks; lung disease other than asthma; pregnancy; history of cardiac, gastrointestinal, or psychiatric disease; or prior participation in a formal asthma education program.

Protocol, Procedures, and Measurements

Subjects were followed for 7 weeks with five study visits. The study setting was a clinical laboratory; all patients remained under the care of their physicians. The investigators did not change prescribed therapy. Participants were informed that the study's purpose was to examine the effects of asthma monitoring and education. Subjects were given a diary to record daily symptom scores, peak flow, and medication use during a 1-week run-in and the subsequent 6 weeks of the study. Visits with the study coordinator were biweekly, except for the 1-week run-in between the first and second visits. This period established the baseline for peak flow, symptoms, and medication use before randomization. Subjects repeated the run-in if their diary recordings were inadequate. No subject withdrew before randomization. At the end of the run-in, subjects were randomly assigned to continue monitoring only (control condition) or receive the self-management intervention. Except for the study coordinator, all investigators and subjects were blinded to group assignment.

Spirometry was performed at each visit, always after withholding short-acting inhaled beta-agonists for ≥ 6 hours and long-acting beta-agonists for ≥ 12 hours. Measurements at the first visit served as the subject's baseline. **At this visit, subjects were given an electronic peak flow meter (Airwatch; Imetrikus, Carlsbad, California) and a diary.** Subjects were told to record the best of three successive peak flow measurements between 5 and 10 AM and between 4 and 10 PM daily. Diary pages were collected at each visit for comparison of written and stored electronic recordings. Medication monitors were placed on both the inhaled corticosteroid and the albuterol metered-dose inhalers. Induced sputum samples were collected at baseline, the end of run-in, and the final visit.

An advanced practice nurse introduced the asthma self-management intervention at the second study visit, after the run-in period. All subjects in the intervention group received the same information in this 30-minute, individual session that was then reinforced by the study coordinator at the next two biweekly visits. The intervention was designed to simulate an educational encounter between a clinician and a patient. The educator had no contact with subjects after this visit. The feasibility of teaching self-management knowledge and skills in a 30-minute session was validated in an open trial (8).

The intervention included the asthma education components recommended in the National Institutes of Health (NIH) guidelines (7). Basic facts about asthma,

the role of airway inflammation and bronchospasm in causing airflow obstruction and symptoms, and the roles and actions of anti-inflammatory and quick relief medications were explained with models and illustrations. Skills for correct inhalation of medication from a metered-dose inhaler using a spacer and for peak flow measurement were taught and practiced. At subsequent visits, subjects were shown graphs of their peak flow data, emphasizing trends over time. Finally, a simple written asthma action plan, based on peak flow zones, and using the "traffic light" analogy, was provided to each intervention subject (7). No attempt was made to change the therapy prescribed by their physicians, and no information about medication compliance was included in the intervention.

Subjects in the control group met with the study coordinator only for data collection and had no contact with any of the other investigators. Control subjects monitored peak flow, symptoms, and medication use, and had the same number of study visits of the same duration. They received no explicit education or instruction about asthma, and no feedback about peak flow data, symptoms, or medication adherence. Instead, visits with the study coordinator focused on collecting diary pages, downloading electronic monitor data, performing spirometry, and sputum induction. All questions about asthma or management were referred to the subject's personal physician.

Outcome Variables and Measurements

To evaluate the effect of the intervention on perceived change in self-management behavior, we asked subjects in both groups at the last study visit to respond to an open-ended question: "Have you made any changes in how you manage your asthma as a result of participating in this study? If so, describe these changes."

Adherence to inhaled corticosteroid medication was assessed as the number of puffs recorded daily in the diary divided by the number of puffs prescribed. Subjects also recorded their daily use (in puffs) of albuterol. The medication monitors, equipped with a microcomputer that recorded and stored 30 days of usage and displayed the number of puffs taken each day, measured the validity of the recorded data (9). Data from the monitors were not concealed from the subjects, but they were not told that it would be compared with the diary records. In cases of discrepancy, the electronic data were considered to reflect actual medication use.

Subjects recorded the severity of asthma symptoms (dyspnea, chest tightness, wheezing, cough, and phlegm production) at the end of each day on validated 10-point numerical rating scales, where 0 = none and 10 = very severe (10–13). The daily symptom score was the sum of the five symptom scores, which was then averaged for each week of the study. Asthma-related quality of life was

assessed at study entry and at the final visit, using a validated questionnaire that assesses the effects of asthma on social, physical, financial, and emotional aspects of respondents' lives (14,15).

The 11-item Perceived Control of Asthma questionnaire, used to assess perceived ability to manage asthma and exacerbations, has high internal consistency (Cronbach $\alpha = 0.74$) and construct validity, correlating strongly with asthma severity, quality of life, and health status (16).

Self-Reported Changes in Behavior

At the final visit, subjects were asked to describe any changes they had made in managing their asthma as a result of participating in the study. This was posed as an open-ended question without prompts.

Pulmonary function parameters (FEV₁ and forced vital capacity) were measured before and after two puffs of albuterol (180 μ g) at every visit, using a spirometer meeting American Thoracic Society standards. Peak flow was measured with a portable electronic meter (17) that stores values for up to 6 months. The device stored the best measurement made within 10 minutes after activation. Diary and electronic data were compared at each visit (18). Morning peak flows were averaged for each 14-day period following each study visit.

Biological markers of airway inflammation included the percentage of eosinophils and neutrophils and the concentrations of eosinophil cationic protein and tryptase in induced sputum samples. The concentrations and cell counts in the samples obtained at the first and second visits were averaged to create mean baseline values and compared with the values at the final visit. Sputum induction, processing, and analysis were performed as described previously (19–21). Eosinophil cationic protein and tryptase concentrations were determined in batched samples by radioimmunoassay (Pharmacia Diagnostics, Inc., Fairfield, New Jersey). The lower limit of detection for the eosinophil assay was 2 ng/mL; for tryptase it was 2 μ g/L.

Statistical Analysis

The primary outcomes were changes (from baseline to final visit) in adherence to inhaled corticosteroid medication, clinical markers of asthma control, and markers of inflammation in sputum samples. Statistical significance for each outcome was set at $P < 0.05$. Between-group comparisons of baseline characteristics were assessed using the chi-squared test (categorical variables) or t test (continuous variables). P values for pooled variances were used when Levine's test for equality of variances had a P value > 0.05 . Self-reported changes in asthma self-management (as proportions reporting the change) were compared using the Fisher exact test. We used analysis of covariance to determine whether changes between the groups were mediated by changes in adherence.

Sample size estimates were based on the estimated effect of the intervention on eosinophil cationic protein and symptom intensity during the study. Preliminary data suggested a 50% reduction (0.67 SD) in the eosinophil cationic protein in the intervention group; no change was expected in the control group. At α (two-tailed) of 0.05 and power of 0.80, the required sample size was 38 subjects. Based on our preliminary data, the effect size for symptom intensity was expected to be 0.58 SD larger than for the control group, yielding a sample size of 48. To allow for potential attrition, we aimed for a sample of at least 54 subjects.

RESULTS

Of 224 adults with asthma who were screened, 68 met study criteria, gave written informed consent, and were enrolled in the study. The most common reasons for exclusion were a history of smoking or inadequate bronchial hyperresponsiveness to inhaled methacholine. Two subjects (1 in each group) developed asthma exacerbations during the study and withdrew, and 1 (in the control group) withdrew because of time constraints. The final sample included 65 subjects: 62 with complete data for all time points and 3 with missing data for one or more outcome variables. There were no significant differences in the characteristics of the subjects in the two groups at baseline (Table 1).

Effects of the Intervention

The educational self-management intervention significantly improved adherence with inhaled corticosteroids and perceived control of asthma, significantly reduced sputum eosinophils, and generally improved indexes of asthma control (Table 2). In the intervention group, adherence to inhaled corticosteroid therapy increased by 30% (from 70% to 91%), whereas it decreased by 5% (from 65% to 62%) in the control group (Table 2, Figure; $P = 0.01$). Perceived control of asthma improved 14% in the intervention group versus 5% in the control group (Table 2; $P = 0.04$). The concentrations of eosinophil cationic protein and tryptase, and the percentage of eosinophils in sputum samples, decreased in the intervention group and increased in the control group. Between-group comparisons showed that only the decrease in eosinophils was statistically significant (67% decrease in the intervention group vs. 17% increase in the control group, $P = 0.02$). Symptom severity and rescue use of beta-agonists decreased, and peak flow and FEV₁ increased, more in the intervention group than in the control group, but in between-group comparisons none of the differences was statistically significant.

Table 1. Baseline Characteristics of Subjects by Study Group

Characteristic	Intervention (n = 33)	Control (n = 32)	P Value
	Number (%) or Mean \pm SD		
Age (years)	32 \pm 9	35 \pm 8	0.22
Female sex	18 (55)	18 (56)	0.54
Education (years)	16 \pm 3	16 \pm 2	0.81
FEV ₁ (% predicted)	80 \pm 18	77 \pm 20	0.51
Asthma duration (years)	21 \pm 10	18 \pm 12	0.31
Symptom severity score (0–50)	11 \pm 6	9 \pm 7	0.26
Nights with symptoms per week	2 \pm 1	2 \pm 1	0.85
Emergency department visits in the last year	1 \pm 1	1 \pm 1	0.41
Perceived asthma control score (11–55)	38 \pm 6	40 \pm 5	0.18
Asthma quality of life (0–80)*	27 \pm 13	24 \pm 14	0.34
Methacholine PC ₂₀ mg/mL [†]	0.57 \pm 0.87	1.04 \pm 2.15	0.29

* Lower scores mean better quality of life.

[†] Provocative concentration of methacholine required to produce a 20% fall in FEV₁. This measurement was available in 27 subjects in the intervention group and 27 in the control group; 6 subjects in the intervention group and 5 in the control group did not meet predetermined criteria for methacholine challenge testing. FEV₁ = forced expiratory volume in 1 second.

Effects of Adherence on Outcomes

The magnitude of the correlation between change in adherence and the change in the other outcomes was weak ($r = 0.03$ to 0.24). Thus, adjusting for adherence had little effect on between-group differences (Table 3).

Self-Reported Changes in Behavior

The most frequent change was using an inhaled corticosteroid more regularly, but there was no significant difference between groups (Table 4). Other changes re-

ported more often by the intervention group included improvements in metered-dose inhaler technique, making environmental control changes, purchasing and using dust barriers on mattresses and pillows, and cleaning the house and bedroom of dust.

DISCUSSION

Our results suggest that asthma education is beneficial, even among patients who monitor their asthma. Al-

Table 2. Between-Group Differences in Clinical and Biological Outcomes

Outcome	Intervention (n = 33)		Control (n = 32)		Between-Group Difference in Change from Baseline to Final Visit (95% Confidence Interval)	P Value
	Baseline	Final	Baseline	Final		
	Mean \pm SD					
Adherence to inhaled corticosteroid (%)	70 \pm 30	91 \pm 32	65 \pm 34	62 \pm 38	24 (5 to 43)	0.01
Quality of life*	27 \pm 13	17 \pm 9	24 \pm 14	19 \pm 13	-4.4 (-9 to -0.2)	0.06
Perceived control of asthma	37 \pm 6	42 \pm 5	40 \pm 5	42 \pm 5	2.6 (0.1 to 5)	0.04
Symptom severity	11 \pm 6	8 \pm 7	9 \pm 7	7 \pm 6	-0.9 (-4 to 2)	0.56
Beta-agonist (puffs)	4 \pm 3	3 \pm 3	3 \pm 2	3 \pm 3	-0.9 (-2 to 0.5)	0.21
FEV ₁ (% predicted) [†]	83 \pm 17	90 \pm 16	78 \pm 20	80 \pm 20	5 (-1 to 10)	0.09
Morning peak flow (L/min)	446 \pm 125	461 \pm 123	367 \pm 107	363 \pm 97	19 (-3 to 52)	0.23
Eosinophil cationic protein (ng/mL) [‡]	319 \pm 277	231 \pm 203	340 \pm 362	324 \pm 346	-72 (-8 to 63)	0.29
Tryptase (μ g/L) [†]	10 \pm 22	5 \pm 9	5 \pm 8	3 \pm 5	-4 (-9 to 2)	0.17
Eosinophils (%) [‡]	6 \pm 8	2 \pm 2	6 \pm 7	7 \pm 12	-5 (-8 to -1)	0.02
Neutrophils (%) [‡]	39 \pm 17	37 \pm 25	40 \pm 19	44 \pm 19	-6 (-15 to 3)	0.21

* Lower scores mean better quality of life.

[†] Available in 31 patients at both time points in the control group.

[‡] Available in 29 patients at both time points in the control group.

FEV₁ = forced expiratory volume in 1 second.

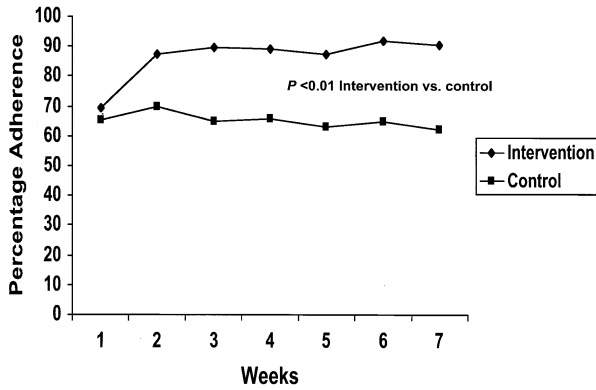


Figure. Changes in adherence to inhaled corticosteroid therapy among subjects in the intervention and control groups.

though the subjects in the control group recorded peak flow and completed diaries as often as did subjects in the intervention group, they did not improve adherence to inhaled corticosteroids. However, the control group did not wane in adherence, as has been seen in recent observational studies (22,23). Indeed, compliance was often better than expected in clinical trials, which may account for the frequent finding of improvements in asthma control in subjects treated with placebo (24,25).

We cannot be certain which component of the intervention was most responsible for the clinical improvements in the intervention group, as several behaviors improved, including use of inhaled corticosteroids, improved inhaler technique, and instituting environmental control measures, such as cleaning the house and bedroom of dust and covering the bedding with dust barriers, more often than did the control subjects.

Table 4. Self-Described Changes in Self-Management Behavior after Study Participation

Change	Intervention	Control	P Value
	(n = 31)	(n = 27)	
	Number (%)		
Use inhaled steroid regularly at prescribed dose	25 (81)	17 (63)	0.11
Improved inhaler technique	11 (36)	2 (7)	0.01
Using spacer with inhaler	4 (13)	0	0.07
Keeping peak flow record	3 (10)	3 (11)	0.60
Monitoring peak flow regularly	12 (39)	12 (44)	0.43
Made environmental control changes	14 (45)	5 (26)	0.03
Put dust barriers on bed/pillows	8 (26)	1 (3)	0.02
Cleaning house/bedroom of dust	11 (36)	0	0.001
Keeping animals out of bedroom	2 (7)	1 (4)	0.55
Identified/avoided asthma triggers	9 (29)	4 (15)	0.16

Regular use of inhaled corticosteroid therapy improves asthma control (26–32), but the improvements in our other outcomes were independent of the improvement in adherence. Training each subject in the essentials of asthma self-management, in the purposes and uses of different therapies, and providing feedback about changes in their peak flow and spirometry findings, all may have contributed to the benefits of intervention. Providing patients with information about the degree of their airflow obstruction may have influenced behavior, especially if the improvement was also noted subjectively (33).

Table 3. Between-Group Differences after Adjusting for Adherence to Inhaled Corticosteroids*

Outcome	Correlation with Change in Corticosteroid Adherence (r)	Adjusted Between-Group Difference in Change from Baseline to Final Visit (95% Confidence Interval)	P Value
Quality of life [†]	-0.08	-4 (-9 to 1)	0.08
Perceived control of asthma	0.05	3 (0.1 to 5)	0.04
Symptom severity	-0.07	-0.7 (-4 to 3)	0.67
Rescue beta-agonist (puffs)	-0.03	-0.9 (-2.2 to 0.5)	0.22
FEV ₁ (% predicted)	0.16	4 (-1.6 to 9.6)	0.16
Morning peak flow (L/min)	0.23	12 (-22 to 45)	0.50
Eosinophil cationic protein (ng/mL)	-0.22	-39 (-180 to 102)	0.60
Tryptase (μg/L)	-0.03	-4 (-9 to 2)	0.18
Eosinophils (%)	-0.05	-5 (-9 to -1)	0.02
Neutrophils (%)	-0.24	-3 (-13 to 6)	0.48

* See footnotes to Table 2 for Ns of measurements.

[†] Lower scores mean better quality of life.

FEV₁ = forced expiratory volume in 1 second.

We also examined the effects of self-management education on sputum markers of inflammation (34–37). The educational intervention led to changes in all inflammatory markers in induced sputum, although only the change in sputum eosinophil percentage, the most widely used marker of asthmatic airway inflammation, was statistically significant. This effect is consistent with the known effects of inhaled corticosteroids on asthmatic airway inflammation (38).

Because individual training is the most effective method of teaching, and because the NIH guidelines recommend that this be provided in the context of care, we examined an intervention that could be taught in 30 minutes, so that it could be added to a medical appointment and reinforced at subsequent visits. Our findings suggest that simple instruction in asthma self-management improves adherence with inhaled corticosteroid use, enhances perceived asthma control, and reduces one marker of airway inflammation, sputum eosinophilia. Whether these improvements will be maintained, and whether this training reduces asthma morbidity, needs to be addressed.

REFERENCES

- Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for asthma—United States, 1980-1999. *MMWR Morb Mortal Wkly Rep.* 2002;51:1–13.
- Wilson SR, Scamagas P, German DF, et al. A controlled trial of two forms of self-management education for adults with asthma. *Am J Med.* 1993;94:564–576.
- Bailey WC, Richards JM Jr, Brooks CM, et al. A randomized trial to improve self-management practices of adults with asthma. *Arch Intern Med.* 1990;150:1664–1668.
- Ignacio-García JM, Gonzalez-Santos P. Asthma self-management education program by home monitoring of peak expiratory flow. *Am J Respir Crit Care Med.* 1995;151:353–359.
- Kotses H, Bernstein IL, Bernstein DI, et al. A self-management program for adult asthma. Part I: development and evaluation. *J Allergy Clin Immunol.* 1995;95:529–540.
- Kotses H, Stout C, McConnaughy K, et al. Evaluation of individualized asthma self-management programs. *J Asthma.* 1996;33:113–118.
- National Asthma Education and Prevention Program. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, MD: National Institutes of Health; 1997.
- Janson S, Hardie G, Fahy JV, Boushey HA. Use of biological markers of airway inflammation to detect the efficacy of nurse-delivered asthma education. *Heart Lung.* 2001;30:39–46.
- Simmons M, Nides MA, Kleerup MD, et al. Validation of the Doser™, a new device for monitoring metered-dose inhaler use. *J Allergy Clin Immunol.* 1998;102:409–412.
- Janson-Bjerkli S, Shnell S. Effect of peak flow information on patterns of self-care in adult asthma. *Heart Lung.* 1988;17:543–549.
- Janson-Bjerkli S, Ferketich S, Benner P. Predicting the outcomes of living with asthma. *Res Nurs Health.* 1993;16:241–250.
- Haahtela T, Jarvinen M, Kava T, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med.* 1991;325:388–392.
- Beasley R, Cushley M, Holgate ST. A self-management plan in the treatment of adult asthma. *Thorax.* 1989;44:200–204.
- Marks GB, Dunn SM, Woolcock AJ. A scale for the measurement of quality of life in adults with asthma. *J Clin Epidemiol.* 1992;45:461–472.
- Gupchup GV, Wolfgang AP, Thomas J III. Reliability and validity of the asthma quality of life questionnaire—marks in a sample of adult asthmatic patients in the United States. *Clin Ther.* 1997;19:1116–1125.
- Katz PP, Yelin EH, Eisner MD, Blanc PD. Perceived control of asthma and quality of life among adults with asthma. *Ann Allergy Asthma Immunol.* 2002;89:251–258.
- Martin R, Pak J, Kunselman MA, Cherniack RM. Asthma Clinical Research Network. Assessment of the AirWatch™ lung function monitoring system. *J Allergy Clin Immunol.* 1999;103:535–536.
- Hyland ME, Kenyon CA, Allen R, Howarth P. Diary keeping in asthma: comparison of written and electronic methods. *BMJ.* 1993;306:487–489.
- Gershman NH, Wong HH, Liu JT, et al. Comparison of two methods of collecting induced sputum in asthmatic subjects. *Eur Respir J.* 1996;9:2448–2453.
- Wong HH, Fahy JV. Safety of one method of sputum induction in asthmatic subjects. *Am J Respir Crit Care Med.* 1997;156:299–303.
- Fahy JV, Steiger DJ, Liu J, et al. Markers of mucus secretion and DNA levels in induced sputum from asthmatic and from healthy subjects. *Am Rev Respir Dis.* 1993;147:1132–1137.
- Apter AJ, Reisine ST, Affleck G, et al. Adherence with twice-daily dosing of inhaled steroids: socioeconomic and health-belief differences. *Am J Respir Crit Care Med.* 1998;157:1810–1817.
- Apter AJ, Boston RC, Norfleet GM, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. *J Allergy Clin Immunol.* 2003;111:1219–1226.
- Kienle GS, Kiene H. Placebo effect and placebo concept: a critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. *Altern Ther.* 1996;2:39–54.
- Moyad MA. The placebo effect and randomized trials: analysis of conventional medicine. *Urol Clin North Am.* 2002;29:125–133.
- Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis.* 1996;148(suppl):S1–S26.
- Dahl R, Lundback E, Malo JL, et al. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. *Chest.* 1993;104:1352–1358.
- Fabbri L, Burge PS, Croonenborgh L, et al. Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. *Thorax.* 1993;48:817–823.
- Gustafsson P, Tsanakas J, Gold M, et al. Comparison of the efficacy and safety of inhaled fluticasone 200 mcg/day with inhaled beclomethasone dipropionate 400 mcg/day in mild and moderate asthma. *Arch Dis Child.* 1993;69:206–211.
- Haahtela T, Harvinen M, Kava T, et al. Comparison of beta₂-agonist, terbutaline, with an inhaled corticosteroid, budesonide in newly detected asthma. *N Engl J Med.* 1991;325:288–392.
- Jeffery PK, Godfrey RW, Adelroth E, et al. Effects of treatment of airway inflammation and thickening of basement membrane reticular collagen in asthma. *Am Rev Respir Dis.* 1992;145:890–899.
- van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, et al. Effects of 22 months of treatment with inhaled corticosteroids and/or beta₂-agonist on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis.* 1992;146:547–554.

33. Bandura A. *Social Foundations of Thought and Action: A Social Cognitive Theory*. Englewood Cliffs, NJ: Prentice Hall; 1986.
34. Fahy JV, Wong H, Liu J, Boushey HA. Comparison of samples collected by sputum induction and bronchoscopy from asthmatic and healthy subjects. *Am J Respir Crit Care Med*. 1995;152:53–58.
35. Pin I, Freitag AP, O'Byrne M, et al. Changes in the cellular profile of induced sputum after allergen-induced asthmatic responses. *Am Rev Respir Dis*. 1992;145:1265–1269.
36. Fahy JV, Liu J, Wong H, Boushey HA. Analysis of cellular and biochemical constituents after allergen challenge: a method for allergic inflammation. *J Allergy Immunol*. 1994;93:1031–1039.
37. Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol*. 1995;95:843–852.
38. Roisman GL, Peiffer C, Lacroque JG, et al. Perception of bronchial obstruction in asthmatic patients. Relationship with bronchial eosinophilic inflammation and epithelial damage and effect of corticosteroid treatment. *J Clin Invest*. 1995;96:12–21.