

Predictors of protocol adherence in a pediatric asthma clinical trial

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Background: Declining protocol adherence can threaten the validity of a clinical trial.

Objective: We sought to explore patient and family factors important for protocol adherence in the 133 patients followed at one of the 8 Childhood Asthma Management Program (CAMP) clinical centers. Difficulties with timely return of diary cards (diary card problem), with keeping or frequently rescheduling appointments (appointment problem), and with commitment to all aspects of the trial (commitment problem) were tracked prospectively during the treatment phase of CAMP, which ranged from 20 to 40 months at the time of the analysis.

Methods: We performed a cross-sectional analysis.

Results: During the course of this investigation, no St Louis CAMP patients dropped out of the study, although signs of eroding participation were observed in 44% of patients. For this cross-sectional analysis, the percentage of patients exhibiting protocol-adherence problems was greater the longer patients had been in the trial: 33.3% at 20 to 25 months, 39.5% at 26 to 30 months, 51.4% at 31 to 35 months, and 69.2% at 36 to 40 months ($P < .01$). The diary card problem was present in 22.2% of the patients enrolled in the trial for 20 to 25 months compared with 66.7% for patients enrolled for 36 to 40 months ($P < .005$). Appointment and commitment problems were present in smaller percentages of patients and did not change by time in the trial ($P = .41$ and $.22$, respectively). A logistic regression analysis of demographic characteristics indicated that age at randomization and time in the trial were significant factors: for every 2-year increase in age, a child was twice as likely to have a commitment problem (odds ratio [OR], 1.96; 95% CI, 1.50-2.57), and for each additional 5 months of participation in the study, a child was twice as likely to have a diary card problem (OR, 1.91; 95% CI, 1.76-2.07). There was no influence of family income, patient race, or patient sex on the occurrence of any of the 3 protocol-adherence problems. A similar analysis of psychologic characteristics of the child and family indicated (1) a 2-fold increase in

the risk of a diary card problem with a 10% increase in the percentage of total commissions on the attention scale of the Gordon Diagnostic Study (OR, 2.18; 95% CI, 2.02-2.35), (2) a 2-fold decrease in the risk of an appointment problem with a 10-unit increase in the Child Manifest Anxiety Scale (OR, 0.46; 95% CI, 0.44-0.49), (3) a 2-fold decrease in risk of an appointment problem with a 10-unit increase in the cohesion subscale of the Family Environment Scale (OR, 0.58; 95% CI, 0.55-0.60), and (4) a 5-fold decrease in the risk of a commitment problem with a 10-unit increase in the Child Depression Index score (OR, 0.21; 95% CI, 0.18-0.24).

Conclusions: Adherence and retention problems commonly occur in longer clinical trials. CAMP patients and families were selected in part on the basis of likelihood of being able to participate in the trial to enhance the conclusions of the trial. Despite this selection process, adherence problems were noted. Problems increased with duration of participation, increasing child age, and the presence of less family cohesion or attention problems in the child. In contrast, the presence of mild emotional distress (anxiety and depression) in the child was associated with fewer protocol-adherence problems. Incorporating procedures that help anticipate and identify adherence problems early might improve continued participation in all aspects of a trial and even retention in long-term clinical trials. (*J Allergy Clin Immunol* 2002;110:596-602.)

Key words: Adherences, pediatric asthma clinical trial, retention

The lives of 2 to 5 million children in the United States are directly affected by asthma, the most common chronic disease of childhood.¹ Over the past few decades, medications have been developed to treat and prevent asthma symptoms. Asthma can be managed effectively by adherence to medication regimens designed to prevent morbidity and mortality. Poor adherence to the medical regimen is associated with significant adverse outcomes. Treatment failures evidenced by regular asthma symptoms occur at a much higher rate for those patients who do not use medications as prescribed.²⁻⁴ In clinical trials treatment nonadherence dilutes findings and can lead to erroneous conclusions.⁵

Better adherence in clinical trials can facilitate more accurate research and better identify effective therapies for asthma. Examination of underlying causes of nonadherence by patients in clinical trials might yield information that could improve participation and even retention, which often has been as low as 75% after periods of as short as 12 weeks to 1 year.⁶⁻⁸

This study explores the association of patient and family characteristics with problems in protocol adherence in the subset of patients followed at one of 8 clinical centers in a pediatric asthma clinical trial, the Childhood Asthma

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Abbreviations used

CAMP:	Childhood Asthma Management Program
CDI:	Children's Depression Inventory
FES:	Family Environment Scale
GDS:	Gordon Diagnostic System
OR:	Odds ratio
RCMAS:	Revised Children's Manifest Anxiety Scale
WISC-III intelligence test:	Wechsler Intelligence Scale for Children, Third Edition

Management Program (CAMP). We evaluated overall adherence with certain requirements of the clinical trial: completion and timely return to the clinical center of diary cards, keeping appointments, and commitment to completion of all aspects of the trial. We hypothesized that responses to questionnaires about family and individual psychosocial functioning, which were administered before randomization into the trial, would correlate with dimensions of nonadherence in trial activities. Identification of such psychologic characteristics of the patient and family might help to identify patients at risk for nonadherence in clinical trials.

METHODS

Patients

This ancillary study included all 133 patients participating in the St Louis CAMP center. All participants provided written consent for CAMP. Because the ancillary study required no data collection from the patient beyond those data collected as part of the main trial, the St Louis institutional review board did not require a separate consent for the ancillary study. CAMP was a 5-year, multicenter clinical trial funded by the Division of Lung Diseases of the National Heart, Lung, and Blood Institute of the National Institutes of Health.⁹ The primary goal of CAMP was to study the effects of regular inhaled anti-inflammatory therapy on growth of lung function in children 5 to 12 years of age at the time of randomization. On entry into the trial, the patients were randomized into one of 3 treatment groups: (1) budesonide plus as-needed albuterol, (2) nedocromil plus as-needed albuterol, and (3) placebo for either budesonide or nedocromil plus as-needed albuterol. During the screening period before randomization, likelihood of adherence to study procedures was assessed, and baseline data were collected.⁹ As part of the consent process, patients and families were told that they could withdraw at any time and refuse participation in any portion of the trial while still remaining in CAMP. After randomization, the patients were seen at 2 months, 4 months, and then every 4 months thereafter. At each of these visits, diary cards were reviewed, interval histories were obtained with questions concerning interval symptoms, height and weight were measured, and spirometry was performed. A physical examination and methacholine challenge were performed annually. As a component of the research protocol, patients and parents completed psychologic questionnaires annually. Participation in CAMP included attendance at visits, completion of daily diaries, and use of a trial medication daily. These expectations for involvement in the trial are similar to other long-term trials in pediatric asthma. In addition, to maintain interest and satisfaction with the trial, CAMP staff provided social events twice yearly. Although these activities were voluntary, participation in the social activities was viewed by the CAMP staff as an indicator of attachment of the child and family to the trial.

The 133 St Louis CAMP patients were 5 to 12 years old at randomization and 7 to 16 years old (median, 11 years) at the time of data analysis. Forty percent were female, and 17% were of minority ethnicity (11% black, 3% Hispanic, and 3% other). Asthma severity was mild to moderate at randomization on the basis of the definition of the CAMP screening criteria.⁹ On average, patients had FEV₁ values in the normal range before bronchodilator use (FEV₁ percent predicted: median, 95%; range, 56%-122%). They had significant bronchial hyperresponsiveness to methacholine (PC₂₀FEV₁: median, 1.5 mg/mL; range, 0.1-13.3 mg/mL; an error in software calculation of PC₂₀FEV₁ allowed enrollment of children with a value somewhat higher than the ≤12.5-mg/mL cut-off value for eligibility). Demographic characteristics of patients' primary care givers are given in Table I.

Measures of psychologic function

The following instruments were administered during the screening phase to evaluate the psychologic effect that is associated with mild-to-moderate asthma in childhood. Only tests and questionnaires with well-established capacity to measure behavior, emotions, relationships, and abilities were selected.

Child and family psychologic adaptation

1. The Child Behavior Checklist¹⁰ was completed by the parent or primary care giver to provide information about the child's maladaptive behaviors.
2. The Children's Depression Inventory (CDI)¹¹ and the revised Children's Manifest Anxiety Scale (RCMAS)¹² allowed the child to report depressive or anxious feelings.
3. The Family Environment Scale (FES)¹³ was completed by the parent or primary care giver to assess family cohesiveness and functioning. The subscales for the FES are Cohesion, Expressiveness, and Conflict in the Relationship area; Independence, Achievement Orientation, Intellectual-Cultural Orientation, Active-Recreational Orientation, and Moral-Religious Emphasis in the Personal Growth area; and Organization and Control in the System Maintenance area.
4. The Impact on Family Scale¹⁴ and the Medical Outcomes Study Social Support Survey¹⁵ assessed parent or care giver perception of the degree to which the child's illness had a detrimental effect on the family.

Cognitive

The Wechsler Intelligence Scale for Children, Third Edition (WISC-III intelligence test) was used to evaluate general intellectual skills. Short forms of the WISC-III and the Wechsler Preschool and Primary Scale of Intelligence, Revised, which have been found to correlate well with standard long-form scores,¹⁶ were used. The Gordon Diagnostic System (GDS),¹⁷ a battery of self-regulation and attention tests that measure impulse control and simple-complex vigilance, was administered to each patient.

Tracking of protocol-adherence problems

The coordinator evaluated patients and families at each visit to identify difficulties with adherence to the CAMP protocol that the team considered indicators of risk for attrition from the trial. Coordinators tracked and recorded problems with diary card completion and return, keeping appointments, and commitment to all aspects of the trial at each patient visit and entered the data into a database constructed for this purpose. At the end of April 1997, the time of our analysis, 45 patients had been in the trial for 20 to 25 months, 38 for 26 to 30 months, 37 for 31 to 35 months, and 13 for 36 to 40 months.

Data on protocol-adherence problems were collected by using a regimen specific to each category.

TABLE I. Characteristics of primary care giver of CAMP patients in the St Louis center (n = 133)

Female sex	89%
Has a partner	86%
Works outside of home	76%
Highest education level of primary care giver	
Did not complete high school	2%
Completed high school	19%
Some college or postsecondary education or training	43%
Completed college	37%
Highest education level of partner of primary care giver (n = 115)	
Did not complete high school	3%
Completed high school	18%
Some college or postsecondary education or training	30%
Completed college	49%
Annual household income level	
<\$15,000	5%
\$15,000-\$29,999	19%
\$30,000-\$49,999	28%
≥\$50,000	45%
Unknown	4%

Diary card problems. Diary card problems took into account only information for the 12 months ending in April 1997. Patients were issued a 4-month supply of 8 cards with 10 postage-paid and addressed envelopes and instructed to return each card to the center on completion. Each diary card recorded 2 weeks of data: asthma symptoms (with a code from 0-3), the best of 3 morning peak flow values, the best of 3 evening peak flow values, nighttime awakenings caused by asthma, absence from school caused by asthma, contact with doctor or emergency department, use of albuterol for symptoms, use of albuterol as pretreatment for exercise, use of prednisone for an exacerbation, and use of the twice daily trial medication. The cards were to be mailed after completion and were due within 6 weeks. Coordinators kept track of arrival dates of incoming diary cards for their patients; when a card was received, the date of receipt was affixed and reviewed by the coordinator. Diary card problems were categorized only by time of receipt and not by completeness of the data items on the card. Diary card protocol-adherence problems were defined as follows:

1. Late diary cards: more than 50% of the 1-year supply (24 cards covering the period from May 1996 through April 1997) of a patient's diary cards were returned to the center more than 6 weeks overdue. Lateness was recorded in the retention file when diary cards were received.
2. Missing diary cards: 3 or more of a patient's required 24 cards within the period from May 1996 through April 1997 were not returned. The number of missing cards was recorded in the retention file.
3. Refusal to keep diary cards: the patient stated that diary cards would no longer be completed as part of his or her participation in CAMP. Refusal was noted in the progress notes of the patient's chart at the time of a visit, as well as in the retention file.

The coordinator would review the diary card return sheet before every patient's clinic visit. The coordinator would note whether a patient refused to complete the cards and review the issue with the patient at each visit.

Appointment problems. Data for appointment and commitment problems considered all appointments and opportunities to express commitment to the trial from randomization through April 1997. Appointment problems were defined as follows:

1. Frequent cancellations and rescheduling: families canceled and

rescheduled one or more appointments per year on average over the time of the trial (33% of all appointments since randomization). Cancellations were logged in the patient's chart, noting date called, date appointment scheduled, and reason for canceling.

2. Not showing for an appointment: patient failed to appear for a scheduled appointment without calling in advance. No-shows were logged in a schedule book by the secretary and in the retention file.

All appointment problems were noted on the patient's retention file and reviewed at each clinic visit.

Commitment problems. On enrollment into CAMP, all patients made a commitment for 5 years of participation. CAMP patients and families were asked to participate in all aspects of routine CAMP visits and data collection. In return, patients received asthma care from the CAMP staff, asthma education, and all medications at no cost. Commitment problems were recorded in the chart and on the retention file by the patient's coordinator at each visit. Commitment problems were defined as follows:

1. Data-collection refusal: family refused to participate in one or more (but not all) CAMP procedures, such as the annual methacholine challenge or yearly psychologic testing. All patients and families had completed psychologic testing before randomization.
2. Poor attendance at CAMP social functions: at each CAMP event, patients were required to sign in and take a name tag, and hence attendance was determined. Poor attendance was considered when the patient attended less than one third of the semi-annual CAMP functions on average over the time of the trial.
3. Voiced dissatisfaction with participation in CAMP: patient or family indicated dissatisfaction with their participation in CAMP. If a patient refused to complete all CAMP procedures except for the interview or voiced dissatisfaction with CAMP, it was recorded in the retention file at the time of the visit or at the time of the occurrence. When a patient or family expressed dissatisfaction, the reasons were explored fully, and an attempt was made to address the family's concern. Concern about a certain procedure might have resulted in a decision not to require the child to do the procedure or restarting a task at a later time. No patient was prevented from withdrawing from the study if that was a firm desire of the family.

Analysis of data

For Tables II and III, χ^2 and t tests were used to make comparisons of interest, respectively. A backward logistic regression analysis was performed in the likelihood of any problem occurring for each type of protocol-adherence problem, assessing the relative contributions of the demographic characteristics of age in years at randomization, sex (male vs female), income (<\$50,000 vs ≥\$50,000), ethnicity (non-Hispanic white, 110, vs other, 23), and months in study. Odds ratios (ORs) with 95% CIs were calculated for each factor remaining in the final regression model at a P value of .05 or greater. There were no significant interactions between factors. All analyses were conducted with the SAS statistical software system (SAS Version 6.12, 1996; SAS Institute, Inc, Cary, NC). A similar approach was used to assess the relative contributions of psychologic measures, Child Behavior Checklist, CDI, Impact on Family Scale, RCMAS, FES (cohesion, conflict, control, and organization, each as a distinct risk factor), WISC-III (estimated IQ), and GDS on the risk of a diary card, appointment, or commitment problem. GDS was assessed as total commissions divided by total responses times 100% or total commissions as a percentage of total responses.

TABLE II. Diary card problems, appointment problems, and commitment problems by time in CAMP

	Months in trial				P value
	20-25 (n = 45)	26-30 (n = 38)	31-35 (n = 37)	36-40 (n = 13)	
Any problem*	33.3%	39.5%	51.4%	69.2%	<.01
Diary card problems*					
Late	20.0%	26.3%	43.2%	61.5%	
Missing	11.1%	13.1%	24.3%	30.7%	
Refuse	4.4%	2.6%	8.1%	0.0%	
Any problem	22.2%	28.9%	40.5%	66.7%	<.005
Appointment problems*					
Cancellations-rescheduling	13.3%	13.1%	18.9%	15.4%	
No shows	4.4%	2.6%	5.4%	7.7%	
Any problem	15.6%	13.2%	21.6%	23.1%	.41
Commitment problems*					
Poor attendance at social functions	6.6%	7.9%	13.5%	7.7%	
Data refusal	4.4%	2.6%	5.4%	7.7%	
Dissatisfaction with study	6.6%	7.9%	10.8%	0.0%	
Any problem	11.1%	13.2%	21.6%	15.4%	.22

*Percentage of patients in trial for this length of time.

TABLE III. Psychologic measure mean scores by problem type

Risk Factor	Problem type								
	Diary Card			Appointment			Commitment		
	Y (mean ± SD)	N (mean ± SD)	P value	Y (mean ± SD)	N (mean ± SD)	P value	Y (mean ± SD)	N (mean ± SD)	P value
CBCL	51.3 ± 9.3	51.4 ± 7.6	.96	53.7 ± 7.0	50.0 ± 8.4	.15	52.5 ± 6.1	51.1 ± 8.6	.49
CDI	6.6 ± 6.2	5.9 ± 5.1	.49	4.0 ± 4.4	6.5 ± 5.6	.05	3.6 ± 3.8	6.5 ± 5.6	.005
IFS	35.9 ± 14.5	32.2 ± 9.4	.12	32.2 ± 11.4	33.7 ± 11.5	.58	32.5 ± 13.2	33.6 ± 11.2	.69
RCMAS	44.9 ± 10.3	45.0 ± 10.3	.98	39.2 ± 10.6	46.1 ± 9.9	.003	40.4 ± 9.9	45.8 ± 10.1	.03
WISC-III	105.1 ± 13.5	106.4 ± 14.2	.60	108.5 ± 12.3	105.5 ± 14.2	.35	109.8 ± 14.4	105.3 ± 13.8	.18
GDS	0.48 ± 0.04	0.46 ± 0.05	.04	0.48 ± 0.04	0.46 ± 0.05	.11	0.47 ± 0.05	0.47 ± 0.05	.73
GDS as percentage	48.0 ± 4.4	46.1 ± 5.4	.04	48.4 ± 3.9	46.5 ± 5.3	.11	47.1 ± 4.6	46.7 ± 5.2	.73
FES*	54.7 ± 5.2	54.8 ± 5.5	.97	53.1 ± 5.9	55.1 ± 5.3	.12	54.4 ± 5.0	54.8 ± 5.5	.74
FES Cohesion measure	58.9 ± 11.2	59.1 ± 10.9	.93	54.6 ± 13.2	59.9 ± 10.3	.04	59.0 ± 9.2	59.1 ± 11.3	.97
FES Conflict measure	48.9 ± 11.8	49.4 ± 11.3	.82	48.6 ± 12.7	49.3 ± 11.2	.80	46.6 ± 11.0	49.7 ± 11.5	.27
FES Organization measure	55.0 ± 11.8	54.9 ± 11.0	.98	55.3 ± 11.4	54.8 ± 11.2	.86	57.2 ± 9.9	54.5 ± 11.4	.34
FES Control measure	56.0 ± 8.4	55.6 ± 9.8	.81	53.9 ± 9.3	56.1 ± 9.3	.29	54.8 ± 8.1	56.0 ± 9.5	.60

Y, Yes, risk factor present; N, no, risk factor not present; CBCL, Child Behavior Checklist; IFS, Impact on Family Scale.

*Average of the 4 FES measures.

RESULTS

At the time of analysis (20-40 months in the trial), 44% of the 133 patients had at least one of the 3 types of protocol-adherence problems, 8% had 2 types of problems, and 9% had all 3 types of problems. A total of 88 protocol-adherence problems were identified in the 133 patients. Difficulty with diary card requirements was the most frequent problem (52% of the 88 total problems), followed by difficulty with appointments (26%) and commitment (22%). Of the patients with only a single problem, 67% had difficulty with diary card requirements.

For the cross-sectional analysis, problems overall were greater the longer patients were in the trial, with 33.3% of patients in the trial for 20 to 25 months having a problem, 39.5% for 26 to 30 months, 51.4% for 31 to 35 months, and 69.2% for 36 to 40 months ($P < .01$). Difficulty with

diary card requirements (Table II) was greater in patients enrolled in the trial for 36 to 40 months than for those enrolled for 20 to 25 months ($P < .005$). The latter trend was apparent for both late diary cards and missing diary cards, with late diary cards and missing diary cards occurring in approximately two thirds and one third, respectively, of the patients enrolled for 36 to 40 months. None of the patients in the trial for 36 to 40 months refused to complete diary cards, whereas 4.4% in the trial for 20 to 25 months, 2.6% for 26 to 30 months, and 8.1% for 31 to 35 months refused (Table II).

Appointment and commitment problems were present in smaller percentages of patients and in similar percentages of patients in the trial for increasing lengths of time ($P = .41$ and $.22$, respectively; Table II). Frequent cancellation occurred in approximately 15% of families and was not significantly different on the basis of time of

Asthma, rhinitis,
other respiratory
diseases

enrollment. Regardless of time in the study, only a small percentage of families (2.6%-7.7%) did not keep scheduled appointments (Table II). Refusal to allow collection of data and expression of dissatisfaction with the trial (Table II) occurred in small percentages of patients and was not present in a greater percentage of patients in the trial for longer periods of time.

Although there were increasing numbers of patients exhibiting protocol-adherence problems with increasing time in the study, patients displaying one or more problems were enrolled for similar durations as for patients without a problem (mean $\pm$ SD of 29.8 ± 5.2 months and median of 31 months vs mean $\pm$ SD of 27.4 ± 4.7 months and median of 30 months, respectively).

The logistic regression analysis of demographic characteristics indicated that the older a child was at randomization, the more likely the child was to have a commitment problem; for every 2-year increase in age at randomization, a child was twice as likely to have a commitment problem (OR, 1.96; 95% CI, 1.50-2.57). With increasing time in the trial, a child was more likely to have a diary card problem; for each additional 5 months of participation in the study, a child was twice as likely to have a diary card problem (OR, 1.91; 95% CI, 1.76-2.07). There was no influence of family income, patient race, or patient sex on the occurrence of any of the 3 protocol-adherence problems, although female children showed a trend toward being more likely to have a diary card problem ($P = .06$).

Table III shows the results of psychologic tests done before randomization, comparing the mean scores for those with the specified protocol-adherence problem with those of patients without the specified problem. For diary card problems, GDS and GDS as a percentage were different; patients with the problem had more difficulties with self-regulation and attention. For appointment problems, results of CDI, RCMAS, and FES were different between groups; patients with the problem had lower scores on all these tests, indicating less depression and anxiety but less family cohesion. For commitment problems, CDI and RCMAS were different; patients with the problem had less depression and anxiety.

The logistic regression analysis examining the role of psychologic problems of the child and family in the occurrence of protocol-adherence problems indicated 4 measures with significant influence. There was a greater than 2-fold increase in the risk of a diary card problem, with a 10% increase in percentage of total commission errors, reflecting impulsive responding, on the attention scale of the GDS (OR, 2.18; 95% CI, 2.02, 2.35). Indicating protective effects, there was a 2-fold decrease in the risk of an appointment problem with a 10-unit increase in the Child Manifest Anxiety Scale (OR, 0.46; 95% CI, 0.44-0.49) and with a 10-unit increase in the Cohesion subscale of the FES (OR, 0.58; 95% CI, 0.55-0.60). Similarly protective, there was a 5-fold decrease in risk of a commitment problem with a 10-unit increase in the CDI score (OR, 0.21; 95% CI, 0.18-0.24). There was no significant influence of other psychologic measures

on the occurrence of any of the 3 protocol-adherence problems. For each of the 3 protocol-adherence problems, an examination of potential interactions between those psychologic problems and demographic characteristics found influential in the logistic regression analyses above indicated that no combination produced a magnified risk, although the effects were additive; the ORs resulting from these analyses were nearly identical.

DISCUSSION

Clinical trials of long duration are important to a full understanding of the implications of treating chronic pediatric illness. Declining protocol adherence can threaten the validity of a trial. To prevent this, long-term trials require additional resources to (1) carefully screen for patients who might be unable to commit to the full duration of the trial, (2) encourage maximum participation from all patients who enter the study, and (3) recognize and intervene where early signs of attrition become apparent. For CAMP, patients and families were required to participate in a 4-visit screening period to evaluate commitment and capacity to complete the study regimen. To maximize retention in the St Louis CAMP center, even among those patients who complete successfully the extensive screening procedures, staff began tracking details of participation immediately after randomization to obtain early signs of possible attrition for intervention. Although all 133 patients continued to attend visits and perform spirometry for collection of the primary outcome variable, difficulties in adhering to one or more requirements of participation in the trial were observed in 58 (44%) patients followed at the St Louis CAMP center. There was an increased risk for occurrence of a protocol-adherence problem with longer times in the trial and with increased age of the child at randomization. The relationships between the presence of difficulty in adhering to trial requirements and time in the trial and age at randomization are consistent with observations in measurement of adherence of both medication use and overall adherence in other clinical trials.¹⁸

Although patients in St Louis had psychologic test scores in the normal range, which was similar to the scores of CAMP patients overall,¹⁹ several psychologic variables were significantly associated with protocol-adherence problems. Scores on the Impulse subscale of the GDS, the Cohesion subscale of the FES, the RCMAS, and the CDI were associated with difficulty in adhering to requirements of the trial, although not in every case in expected directions. Contrary to expectations, children with increased reports of mood difficulties were stronger participants. Increases in child-reported anxious and depressive symptoms were associated with a lower incidence of appointment problems, and increases in child-reported depressive symptoms were associated with a lower incidence of commitment problems. Although the reasons for these findings are not clear, it is possible that children experiencing mildly increased distress might have found study participation reassuring, in

part because of the emphasis in CAMP on positive communication and supportive relationships with patients.^{20,21} Both difficulties with attention and the absence of family closeness were, as might be expected, predictive of difficulty maintaining participation over time. Patients with lower attention scores, reflecting increased impulsivity errors on the GDS, were more likely to have a diary card problem. Children with attention problems often have difficulty completing school work, and logically, it comes as no surprise that they also had difficulty completing diary cards and adhering to the study protocol. Patients whose families reported less sense of closeness and ability to work together cooperatively, seen in reduced Cohesion scores on the FES, were more likely to demonstrate an appointment problem. Family members who interact more easily and comfortably might also have the necessary capacity to make plans and work collectively to carry them out. Interestingly, the child's intelligence, reflected in the estimated IQ score, was not associated with study participation difficulty, indicating that higher intelligence was not a prerequisite for the capacity to commit to and consistently participate in this longitudinal trial. The lack of effect of IQ on participation in the St Louis CAMP center contrasts with a report from a multicenter, 1-year-long asthma medication trial sponsored by the American Academy of Allergy and Immunology in which decreasing IQ was associated with decreasing retention.²²

At the time the data were collected for this report, all 133 patients randomized in the St Louis CAMP center were still actively involved in the trial, with only 5 of a possible 969 follow-up visits missed; all patients had attended their most recent scheduled visit 20 to 40 months into the trial. Thus description of difficulties in keeping daily diary cards, scheduling and keeping appointments, and commitment to the trial were not associated with actual difficulties in retention, as demonstrated by keeping appointments for collection of primary outcome data. The retention protocol used in this study identified emerging problems and allowed plans to promote retention to be developed for families.

Some of the methods used in the collection and analysis of the data on protocol-adherence problems and the patient population in CAMP limit the application of the findings of study to pediatric asthmatic patients in general. First, the data on collection of problems were collected prospectively but analyzed as an aggregate rather than by time of presentation during the time the child was in the trial. Second, we chose to collapse the data into the 3 major problems for brevity and because of the paucity of outcome events in individual subcategories. It is possible that there was a particular subcategory of a problem that might have been better identified by the demographic and psychologic characteristics of the patients and families. Most important, the role of psychologic and demographic factors in adherence are limited to patients likely to be selected for clinical trials.

Health care providers must help tailor a regimen to individual patient circumstances to ensure optimal care for a

serious chronic illness, such as asthma. It becomes critical to look at all aspects of the regimen, including integration of medication dosing into daily schedules of families. Appreciation and accommodation of individual lifestyles and domestic structures can help in the design and institution of routines that serve to enhance adherence to clinical regimens. The findings that children with increased anxious feelings had fewer difficulties with appointments and children with depression had fewer difficulties with commitment indicate that longitudinal studies need not limit participation to children without problems. Rather, they can develop resourceful and adaptive means of helping even struggling families to maintain participation.

Finally, adherence can be variable and tends to decrease over time. It is important to reassess family circumstances on a regular basis in both clinical trials and clinical practice. Consistent reinforcement, with positive feedback and rapid responses to problems, is critical to maintaining good adherence. Specific patient problems, including failure to complete diary cards or difficulty keeping appointments, might signal increasing risk for dropout from a trial or nonadherence with an individual patient care regimen and hence a need for clinical intervention.²³

REFERENCES

1. Mannino D, Homa D, Akinbami L, Moorman J, Swynn D, Redd S. Surveillance for asthma—United States, 1980-1999. *MMWR Morb Mortal Wkly Rep* 2002;51:1-13.
2. Bender B, Milgrom H, Rand C, Ackerson L. Psychological factors associated with medication nonadherence in asthmatic children. *J Asthma* 1998;35:347-53.
3. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Non-compliance and treatment failure in children with asthma. *J Allergy Clin Immunol* 1996;98:1051-7.
4. Strunk R, Mrazek D, Fuhrmann G, LaBrecque J. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. *JAMA* 1985;254:1193-8.
5. Bender B, Ikle D, DuHamel T, Tinkelman D. Neuropsychological and behavioral changes in asthmatic children treated with beclomethasone dipropionate versus theophylline. *Pediatrics* 1998;101:355-60.
6. Tinkelman D, Reed C, Nelson H, Offord K. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64-77.
7. Skoner D, Szefer S, Welch M, Walton-Bowen K, Cruz-Rivera M, Smith J. Longitudinal growth in infants and young children treated with budesonide inhalation suspension for persistent asthma. *J Allergy Clin Immunol* 2000;105:259-68.
8. Shapiro G, Mendelson L, Kraemer M, Cruz-Rivera M, Walton-Bowen K, Smith K. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol* 1998;102:789-96.
9. Childhood Asthma Management Program Research Group. Design, rationale, and methods. *Clin Trials* 1999;20:91-120.
10. Achenbach T. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington, Vt: University of Vermont, Department of Psychiatry; 1999.
11. Kovacs M. Rating scales to assess depression in school aged children. *Acta Paedopsychiatr* 1981;46:305-15.
12. Reynolds C, Richmond B. Revised Children's Manifest Anxiety Scale (RCMAS). Los Angeles, Calif: Western Psychological Services; 1985.
13. Moos R, Moos B. Family Environment Scale Manual. 2nd Ed. Palo Alto, Calif: Consulting Psychologists Press; 1986.
14. Stein R, Reissman C. The development of an impact-on-family scale: preliminary findings. *Med Care* 1980;18:465-72.
15. Sherbourne C, Stewart A. The MOS social support survey. *Soc Sci Med* 1991;32:705-14.

16. Sattler J. Assessment of children: WISC-III and WPPSI-R Supplement. San Diego, Calif: Jerome M. Sattler Publisher, Inc; 1991.
17. Gordon M, Mettelman B. Technical guide to the Gordon Diagnostic System, model III-R. DeWitt, NY: Gordon Systems, Inc; 1987.
18. Jonasson G, Carlsen K-H, Mowinckel P. Asthma drug adherence in a long term clinical trial. Arch Dis Child 2000;83:330-3.
19. Bender B, Annett R, Ikle D, DuHamel T, Rand C, Strunk R. Relationship between disease and psychological adaptation in children in the Childhood Asthma Management Program and their families. Arch Pediatr Adolesc Med 2000;154:706-13.
20. Childhood Asthma Management Program Research Group. Design and implementation of a patient education center for the Childhood Asthma Management Program. Ann Allergy Asthma Immunol 1998;81:571-81.
21. Childhood Asthma Management Program Research Group. Recruitment of participants in the Childhood Asthma Management Program (CAMP). I: description of methods. J Asthma 1999;36:217-37.
22. Bender B, Ikle D, DuHamel T, Tinkelman D. Retention of asthmatic patients in a longitudinal clinical trial. J Allergy Clin Immunol 1997;99:197-203.
23. Probstfield J, Russell M, Henske J, Reardon R, Insull W. Successful program for recovery of dropouts to a clinical trial. Am J Med 1986;80:777-84.

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