Adherence to Combined Montelukast and Fluticasone Treatment in Economically Disadvantaged African American Youth with Asthma

KELLY A. McNALLY, M.A., JENNIFER ROHAN, M.A., MARK SCHLUCHTER, PH.D., KRISTIN A. RIEKERT, PH.D., PAMELA VAVREK, R.N., AMY SCHMIDT, M.P.H., SUSAN REDLINE, M.D., M.P.H., CAROLYN KERCSMAR, M.D., and DENNIS DROTAR, PH.D.

1Department of Pediatrics, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA
2Department of Psychology, University of Cincinnati, Cincinnati, Ohio, USA
3Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, Ohio, USA
4Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
5University Hospitals Health System, Cleveland, Ohio, USA
6Case Western Reserve University Center for Clinical Investigation, Cleveland, Ohio, USA

High rates of asthma treatment nonadherence have been reported, particularly in economically disadvantaged African American youth. The relationship between adherence to combined medication treatment and asthma outcomes has potential clinical significance but is not well understood. Using electronic monitoring, we describe the pattern of adherence to daily corticosteroid (fluticasone) and leukotriene receptor antagonist (montelukast) medication over the course of 1 year in a population of African American youth with moderate to severe asthma. On average, adherence to montelukast was higher than adherence to fluticasone ($p < 0.01$); however, for both medications, adherence rates significantly declined over the course of the study. After 1 year, participants took only 31% of prescribed doses of montelukast and 23% of prescribed doses of fluticasone. The decline in adherence to both fluticasone ($p < 0.05$) and montelukast ($p < 0.001$) was related to increased healthcare utilization. Furthermore, asthma symptom ratings were related to adherence to montelukast ($p < 0.001$), but not fluticasone adherence. These results suggest that adherence promotion intervention strategies are warranted to improve health-related outcomes in families who are at-risk for treatment nonadherence.

Keywords: treatment adherence; pediatric asthma; health care utilization; compliance; growth curve

INTRODUCTION

Pediatric asthma is an important chronic health condition because of its high prevalence, substantial morbidity, impact on children and families, and medical care costs (1, 2). Although moderate to severe persistent asthma can be controlled by medical treatment (3, 4), rates of morbidity in pediatric asthma (e.g., symptoms, activity limitations, and health care utilization) continue to increase, especially in minority populations (5, 6). One factor implicated in the high rates of asthma-related morbidity is nonadherence to prescribed medical treatment. Previous studies have documented high rates of nonadherence to inhaled corticosteroids (ICS; 50–70%) and relationship with health care utilization (7–10). Previous research has also suggested that children and adolescents with asthma who are from ethnic minority families have higher rates of nonadherence and also demonstrate greater disease severity, more symptoms, school days missed, emergency room visits, and hospitalizations than non-minority children and adolescents (5, 7, 8).

While ICS remains a cornerstone of the treatment of pediatric asthma (4), there is evidence that medications, such as leukotriene receptor antagonists (LTRAs), afford added clinical benefits by reducing airway eosinophilic inflammation and alleviating symptoms of airway obstruction (11–13). The systematic review of Joos et al. (13) found that montelukast as an add-on therapy to ICS improved control of mild to moderate asthma compared with monotherapy of ICS. Moreover, it has been suggested that, compared with ICS, LTRAs such as montelukast may be equally effective in treating pediatric asthma owing to better adherence (14).

Adherence to combined medications (ICS and LTRAs) for pediatric asthma and its relationship to clinical outcomes is not well understood. Several studies have described higher rates of adherence to treatment with an LTRA (montelukast) compared with an ICS such as fluticasone (14–17).

However, one important but as yet unanswered question is, “How does adherence to treatment based on combined medications relate to clinical outcomes?” Understanding the relationship between treatment adherence and asthma control and health outcomes is of primary importance to the clinical management of asthma, as poor clinical outcomes may reflect a need to improve adherence, rather than a need to modify the medication regimen. Information regarding the relationship between adherence and asthma control may help to identify children who are at risk for poor health outcomes based on their patterns of treatment adherence and help practitioners to target adherence promotion interventions to those families.

In one study Rand et al. (17) investigated the relationship between adherence to combined montelukast and ICS treatment and asthma outcomes. The authors found that adherence to fluticasone was positively related to change in pulmonary
functioning but did not relate to use of quick-relief medication or report of symptoms. Adherence to montelukast did not relate to clinical outcomes. However, the implications of the findings for pediatric populations were not clear because pediatric and adult patients (ages 15 to 85 years) were combined and no subgroup analyses of children and adolescents was presented. Moreover, short-term rates of adherence (e.g., 48 weeks) were studied in the context of a controlled clinical trial that compared montelukast with fluticasone (17). Rates of adherence to montelukast and fluticasone and relationship to clinical outcomes in a real-world practice context where both medications are prescribed were not assessed. Finally, Rand et al. (17) did not study African American children and adolescents who are at risk for high rates of nonadherence and asthma-related morbidity (5, 18, 19).

To address these questions, the aim of the present study was to describe the pattern of adherence to combined prescribed treatment (fluticasone and montelukast) over the course of 1 year in a population of economically disadvantaged African American youth. A second aim was to explore the relationship between adherence to fluticasone and montelukast treatment and clinical outcomes, including the frequency of asthma symptoms, use of quick relief medication, and healthcare utilization.

METHODS

Study Design

Data from this study were originally collected to examine the efficacy of a tailored problem-solving intervention in improving adherence to treatment regimens for children with asthma (20). The intervention did not result in any significant group differences in adherence to daily ICS (fluticasone) LTRA (montelukast) treatment, use of quick relief medication for exacerbations, or other relevant clinical outcomes, including asthma-related symptoms and healthcare utilization (21). Consequently, data from the entire sample were pooled for the purposes of the present study. Previous analyses from this combined sample have described quality of life (22, 23), the relationship between risk factors and asthma severity (23), and adherence to treatment for ICS (21).

Recruitment

This study was approved by the Institutional Review Board of the University Hospitals Health Systems. Recruitment strategies included contacting physicians who provided care for children and adolescents with asthma in primary and subspecialty care, inpatient, and emergency room settings in one large pediatric tertiary care center. Parents of patients who met eligibility criteria were first contacted by their physician and then by study staff who explained procedures, obtained parental consent and youth assent, and scheduled appointments. Procedures for electronic monitoring of asthma medication were explained and verified during a home visit. Parents received financial compensation (US$20) for their time and travel to the study visits; children received a gift certificate (US$5) for movie tickets or a meal.

Eligibility Criteria

Children and adolescents were eligible for participation if they were African American between 5 and 17 years of age, diagnosed as having persistent moderate to severe asthma that warranted the prescription of daily ICS (fluticasone) and an LTRA (montelukast) as determined by an evaluation from a study physician based on National Institutes of Health (NIH) guidelines (24) and were from families with incomes below the federal poverty level (25). All participants had been diagnosed with asthma for at least 12 months and were clinically stable before beginning the study.

Prescribed Medical Treatment

In accord with their diagnosis of asthma, eligible patients in the study were evaluated by an asthma specialist who either provided follow-up or consultation to referring physicians who continued to provide care. Participants’ prescriptions included two daily doses of two puffs of preventative ICS (fluticasone) (total of four daily doses) and one daily dose of oral montelukast. All participants were also prescribed albuterol for quick relief symptom control. Fluticasone and albuterol medications were delivered by a metered dose inhaler (MDI). Because we were interested in “real-world” adherence, participants were required to obtain their medication as they had been in the past, which included a co-payment if that was a requirement of their insurance coverage. Medications were not provided to participants.

Predictor Variables: Adherence to Oral Montelukast and Inhaled Fluticasone

Daily adherence to asthma medications was measured using an electronic Drug Exposure Monitor (eDEM) (Aardex) for oral montelukast and a MDILog (West Med Technologies, Englewood, CO) device for inhaled fluticasone. Participants and their families were aware that their medication use was being monitored and they were told how the monitors work. The eDEM records the date and time of each opening of the pill bottle, whereas the MDILog records date and time information for each puff. Validation of these devices has been established (25–27). Adherence was defined as the percent of prescribed medication doses received each day. Recommended quality control procedures for electronic monitoring were followed (28). Data quality was assessed by Rand and her colleagues at Johns Hopkins and included identification of records with broken devices and device malfunctions.

To control for medication “dumping” (i.e., actuating the device several times in a row without inhaling) and overuse, the number of daily montelukast openings was truncated to 1 and number of fluticasone puffs was truncated to 4 (as montelukast is prescribed once daily and fluticasone four times per day). Electronic monitoring data were available for 1 year in 46 (74.1%) participants and 9 to 12 months in 16 (25.9%). Daily medication use data were averaged over 5-day intervals. Thus, a participant with 1 year of monitoring data has 73 time points, where each time point is the average daily fluticasone or montelukast use for that 5-day period.

Outcome Variables: Symptoms, Healthcare Utilization and Rescue Medication Use

Parents were asked to rate their children’s asthma symptoms (e.g., shortness of breath; tightness in the chest; wheezing without a cold; cough; a cold that will not go away; and wheezing with a cold) every 3 months for a 2-week period
on a 5-point Likert scale where a rating of 1 = experiencing symptoms “all of the time” and a rating of 5 = experiencing symptoms “none of the time” was based on the Children’s Health Survey for Asthma (29).

Healthcare utilization was defined as the total number of hospitalizations and emergency room and clinic visits owing to problems with asthma. These data were gathered via self-report and verified by independent chart review at 3-month intervals.

The Doser-CT (Medalogic Corporation), which attached to a MDI and recorded the date and frequency of medication use over the prior 45 days, was used to measure use of quick relief medication (albuterol).

Data Analytic Strategy

Longitudinal adherence and outcome data were analyzed using growth curve or linear mixed models. This approach can be viewed as a two-stage or multilevel modeling approach where for each subject, outcome measures are modeled over time where the regression coefficients are subject-specific random effects. The average curve for the population is represented by the average of the subject-specific curves. Coefficients may also be allowed to depend on additional covariates. The mixed model approach is preferred over traditional repeated-measures analysis of variance in that mixed models can handle missing data points, both continuous and categorical predictors can be incorporated into the model, and appropriate covariance structures can be specified.

Random-effects growth models without additional predictors were fit to describe the average population trajectories as well as within- and between-subject variance components for all variables of interest: montelukast adherence, fluticasone adherence, rescue medication use, symptom ratings, and healthcare utilization. We then examined the relationship between the adherence variables (montelukast and fluticasone) and each outcome variable (rescue medication use, symptom ratings, and healthcare utilization). For these analyses, adherence to fluticasone and montelukast were added as predictors in the models predicting each outcome variable.

The growth curve analysis was conducted using SAS Proc Mixed (SAS Institute, 1990), specifying a linear or quadratic relationship between each outcome and time and allowing the covariance matrix of the random effects (e.g., random intercept, slope, and possibly quadratic coefficient) to be a $2 \times 2$ or $3 \times 3$ unstructured matrix. Both linear and quadratic effects were tested, and in no cases was there a significant quadratic effect. Thus, in further modeling examining covariates, only linear effects were considered. To facilitate interpretation, the time variable was centered at the first occasion so that time 0 represents the first day of monitoring and all predictor variables were centered on the overall mean.

Treatment adherence data are typically analyzed by evaluating overall mean adherence rates for a given study period. To determine whether any additional sensitivity in predicting outcomes was obtained by conducting growth curve modeling, correlational analyses were also conducted between the overall average adherence rates for both medications (i.e., mean percent prescribed) and the outcome variables, averaged over the study period.

Results

Demographic Characteristics

Participants were African American ($N = 63$), ranging in age from 5 to 17 years ($M = 9.71$ years; $SD = 2.69$ years) and were predominantly male ($45 \, [71\%]$). The majority of participating caregivers were African American ($62 \, [98\%]$), the youth’s biological mother ($55 \, [87\%]$), and single ($40 \, [64\%]$). Caregivers ranged from 24 to 71 years ($M = 35.49$ years; $SD = 9.43$ years). Among primary caregivers, $28 \, (44\%)$ had completed high school and $31 \, (50\%)$ were employed at least part-time. The median annual income range of the sample was US$10,000 to $14,999.

Analysis of Sample Attrition

Reasons for failure to complete the study ($N = 21$) included unresponsiveness to contact attempts/failure to show up for appointments ($N = 12$); declining further participation ($N = 1$); less than 270 days of electronic monitoring data available ($N = 5$); and other ($N = 3$).

A comparison of participating families ($N = 63$) with those who failed to complete the study ($N = 21$) indicated no differences with respect to youth age, sex, youth or primary caregiver ethnicity, primary caregiver relationship to youth (i.e., biological mother, biological father, or other). However, families who dropped out had more children under the age of 18 ($M = 4.24$; $SD = 2.00$) compared with participants ($M = 2.86$; $SD = 1.37$), $t(82) = -3.55$, $p < 0.01$, $d = 0.81$ and had a younger age of the primary caregiver (dropouts, $M = 32.14$, $SD = 4.86$; participants, $M = 35.49$, $SD = 9.43$; $t(67.45) = 2.10$, $p < 0.04$, $d = 0.45$). For drop outs, fluticasone adherence data were available for an average of 82.63 days ($SD = 57.82$) and montelukast adherence data were available for an average of 191.14 days ($SD = 128.94$). Average adherence rate (mean percent prescribed) to fluticasone was lower in dropouts ($M = 0.22$, $SD = 0.12$) versus completors ($M = 0.34$, $SD = 0.17$; $t(79) = 3.31$, $p < 0.01$, $d = 0.82$). Similarly, average adherence to montelukast was lower in drop outs (dropouts $M = 0.30$, $SD = 0.25$; completers $M = 0.41$, $SD = 0.21$; $t(82) = 2.04$, $p < 0.05$, $d = 0.48$).

Description of Change in Adherence to Montelukast and Fluticasone Medication

Average montelukast adherence (mean percent prescribed) over the entire study period was 40.99% ($SD = 21.30$) and was significantly higher than the average fluticasone adherence rate ($M = 33.90\%$, $SD = 16.89$; $t(62) = 3.537$, $p < 0.01$, $d = 0.37$).

Figure 1 shows the average montelukast and fluticasone use over time and the growth curve trajectories; Table 1 shows the model estimates. For montelukast adherence, the model intercept indicates that at the onset of the study, participants averaged 0.50 openings per day. Average daily adherence decreased by 0.003 openings per 5-day period, such that after one year, participants took an average of 0.31 doses of montelukast per day, compared with their prescribed dose of 1.

In the model for fluticasone adherence, the intercept indicates that on average, participants took of 1.67 puffs of Flovent per day (42% of prescribed puffs) at the onset of the
Figure 1.—Individual growth curves for montelukast and fluticasone adherence rates. Straight lines represent the growth curve estimates; jagged lines represent the mean adherence rates at each time point.

study. Average daily adherence decreased by 0.010 puffs per 5-day period. After 1 year, participants took an average of 0.933 puffs per day (23.3% of the prescribed puffs per day).

Description of Change in Clinical Outcome Variables: Symptoms, Quick Relief Medication Use and Healthcare Utilization

The results of the growth models for clinical outcomes are also presented in Table 1. For symptom ratings, the average initial symptom rating of 4.23 (of 5) did not significantly change over time. On average, participants took 0.64 puffs per week of albuterol at baseline; and this medication use did not significantly change over time. At the onset of the study, average healthcare utilization was 0.33 visits per 3-month interval, which increased at a rate of 0.01 per week, resulting in an average of 0.75 visits per 3-month interval at the conclusion of the study ($p < 0.06$).

Prediction of Clinical Outcomes Based on Adherence

Given the presence of significant variability in the individual estimates (intercept or slope) for albuterol use, symptom ratings, and healthcare utilization, additional growth curve models predicting these outcomes from montelukast and fluticasone adherence were developed.

As shown in Table 2, montelukast adherence but not fluticasone adherence predicted changes in symptom ratings, based on both intercept ($t[3737.17] = -4.25$, $p < 0.001$) and slope ($t[3736.78] = 3.838$, $p < 0.001$). To probe the interaction, the sample was divided into groups based on the upper and lower quartiles for both montelukast and fluticasone adherence. For montelukast, the “high adherence group” had an average adherence rate of 0.71 (SD = 0.09) and the “low adherence group” had an average adherence rate of 0.17 (SD = 0.05). For fluticasone, the “high adherence group” had a mean adherence rate of 0.62 (SD = 0.08) and the “low adherence group” had an average adherence rate of 0.20 (SD = 0.08). As shown in Figure 2, participants in the low montelukast adherence group (lower quartile of adherence) reported more symptoms, and their symptom ratings worsened over time, while symptoms did not change over time in the high adherence group (upper quartile of adherence). For fluticasone adherence, no effects were found.

Neither montelukast nor fluticasone adherence related to rescue medication use, as evidenced by non-significant effects on the intercept and slope in the model predicting albuterol use (Table 2).

Table 1.—Growth curve models for treatment adherence and clinical outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Intercept (SE)</th>
<th>Rate of change (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast adherence</td>
<td>0.498* (0.028)</td>
<td>-0.003* (0.001)</td>
</tr>
<tr>
<td>Fluticasone adherence</td>
<td>1.668* (0.102)</td>
<td>-0.01* (0.002)</td>
</tr>
<tr>
<td>Albuterol use</td>
<td>0.642* (0.091)</td>
<td>-0.002 (0.002)</td>
</tr>
<tr>
<td>Symptom ratings</td>
<td>4.232* (0.117)</td>
<td>-0.00002 (0.002)</td>
</tr>
<tr>
<td>Healthcare utilization</td>
<td>0.332* (0.132)</td>
<td>0.006 (0.003)</td>
</tr>
</tbody>
</table>

*Significant $p < 0.05$, SE = standard error.

Table 2.—Growth models: predicting clinical outcomes from adherence.

<table>
<thead>
<tr>
<th></th>
<th>Albuterol use Coefficient (SE)</th>
<th>Symptom ratings Coefficient (SE)</th>
<th>Healthcare utilization Coefficient (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average intercept</td>
<td>0.634* (0.093)</td>
<td>4.240* (0.117)</td>
<td>0.314* (0.137)</td>
</tr>
<tr>
<td>Effect of montelukast on intercept</td>
<td>0.070 (0.143)</td>
<td>-0.195* (0.456)</td>
<td>0.424* (0.084)</td>
</tr>
<tr>
<td>Effect of fluticasone on intercept</td>
<td>0.019 (0.039)</td>
<td>-0.006 (0.012)</td>
<td>0.029 (0.023)</td>
</tr>
<tr>
<td>Average rate of change</td>
<td>-0.002 (0.002)</td>
<td>-0.0001 (0.002)</td>
<td>0.006 (0.003)</td>
</tr>
<tr>
<td>Effect of montelukast on rate of change</td>
<td>-0.0004 (0.004)</td>
<td>0.005* (0.001)</td>
<td>-0.008* (0.002)</td>
</tr>
<tr>
<td>Effect of fluticasone on rate of change</td>
<td>-0.0002 (0.001)</td>
<td>-0.0001 (0.0003)</td>
<td>-0.001* (0.001)</td>
</tr>
</tbody>
</table>

*Significant $p < 0.05$, SE = standard error.

Figure 2.—Effect of montelukast adherence on symptom ratings. Individuals with lower montelukast adherence (lower quartile) reported more frequent symptoms over the course of the study (lower values indicate an increase in symptoms) than those with higher montelukast adherence (higher quartile).
ADHERENCE TO COMBINED MONTELUKAST AND FLUTICASONE TREATMENT

The rate of change in healthcare utilization was significantly related to both montelukast and to fluticasone adherence. As illustrated in Figure 3, for both medications, individuals in the low adherence groups increased their healthcare utilization over the course of the study, whereas utilization rates did not significantly change in high adherence groups.

Correlations between Average Adherence Rates and Outcome Variables

To compare and contrast the results of the growth curve analyses to more traditional analysis methods, correlations were examined between average adherence rates over the course of the study and outcome variables. No significant correlations were found between overall mean montelukast adherence rate and average symptom rating ($r = 0.17, p = 0.20$), albuterol use ($r = -0.14, p = 0.30$), and utilization ($r = -0.001, p = 0.99$). Similarly, no significant correlations were present between mean fluticasone adherence rate and average symptom rating ($r = 0.09, p = 0.49$), albuterol use ($r = 0.10, p = 0.44$) and utilization ($r = -0.11, p = 0.39$).

DISCUSSION

To our knowledge, this is the first study to document adherence to combined ICS and LTRA medication treatment of pediatric asthma over a year in a “real world” descriptive study based on electronic monitoring in an economically disadvantaged African American sample. One primary finding was a significant decrease in the trajectory of treatment adherence to ICS over a year. On average, children and adolescents with asthma took less than half of their prescribed medication at the beginning of the monitoring period, and this declined to 20% to 30% after 1 year of study participation. Other studies have documented low rates of treatment adherence to ICS over a year in minority children (7), but this is the first study to evaluate adherence to combined ICS and LTRA based on growth curve analysis and relate adherence to relevant health outcomes. Although the factors that accounted for the high rates of treatment nonadherence were not evaluated here, potential barriers to treatment adherence noted in other studies with minority and low-income children with asthma have included maternal mental health status (30), problematic family allocation of responsibilities for asthma treatment (31), and access to care (19, 32).

Children and adolescents with lower overall rates of treatment adherence to both ICS and LTRA had higher rates of healthcare utilization (combination of emergency room visits, hospitalizations, and clinic visits due to problems with asthma). Other studies have noted similar findings (7, 9) for ICS, but the present study documented this relationship for ICS and LTRA adherence based on growth curve analyses over a sustained period of time. This finding may reflect the generally poorer asthma control that may require intermittent acute interventions in individuals with poor adherence. These results may also suggest that families who are nonadherent to prescribed medication may rely on visits to health care providers for symptom management rather than independently managing symptoms by administering quick relief medication.

Adherence to montelukast medication treatment was related to the frequency of reported symptoms, whereas adherence to ICS was not. This result is particularly interesting given the importance of ICS for pediatric asthma treatment (4). However, these findings may reflect the benefit of increased adherence to montelukast as compared with ICS, which has also been noted in other studies (14–17).

It was noteworthy that no relationship between treatment adherence to combined medications and outcomes were found when analyzing the data by correlations with using mean adherence rates. These findings indicate that the growth
curve data analytic approach (33) provided a more sensitive approach of detecting the relationship between nonadherence and clinical outcomes. This type of statistical approach should be considered when analyzing longitudinal adherence data.

The present findings should be interpreted in light of several methodological limitations. Because we were interested in “real-world” adherence rates, participants were required to obtain their medications as they had in the past; nevertheless, patterns of medication use may have been somewhat changed by virtue of their participation in the study. Participants were compensated a small amount for their participation and were aware that their medication use was being monitored. This may have slightly increased adherence rates, particularly at the beginning of the study; however, given the chronically low adherence rates recorded, it is likely that these effects were minimal. The study is also limited in that information was not available regarding the proportion of participants who had been prescribed fluticasone and montelukast in the past. Patterns of adherence may have differed depending on the novelty of this combined medication regimen.

A further limitation is that, in the absence of an experimental design, it is impossible to isolate the variance in asthma-related clinical outcomes that can be attributed solely to treatment adherence. For example, individual differences in how children with asthma responded to ICS or LTRA treatment owing to genetic and factors other than medication use may have affected outcomes, such as frequency of symptoms (34). In addition, the frequency of sample attrition was high. Moreover, families with more risk factors and more problematic adherence were more likely to drop out of the study, which has been found in other studies (35). The overall rates of adherence to ICS and LTRA treatment may have been even lower and the relationship with outcome variables greater had the entire sample been available for study. For this reason, our findings may underestimate the relationship of treatment adherence to outcomes.

The present findings have a number of implications for future research. For example, the methods of statistical analyses used in this research are well suited for use in studies of long-term trajectories of treatment adherence in pediatric asthma but can also be extended by identifying subgroups of children and adolescents who demonstrate different trajectories of nonadherence and evaluating the relationship of these trajectories to clinical outcomes. In addition, other measures of nonadherence may be sensitive to differences in health outcomes related to asthma. For example, gaps in medication treatment adherence defined as number of consecutive days with no prescribed medication use have been shown to relate to clinical outcomes in adults with asthma (36) and should be studied in pediatric asthma.

Finally, the present findings have potential clinical implications. Our findings suggest that economically disadvantaged African American youth who demonstrate chronically low levels of adherence to ICS and LTRA medication are at-risk for increased health care utilization and problems with asthma control (especially for low LTRA adherence). This high-risk population may be targeted for adherence promotion interventions that are focused specifically on enhancing family management of acute symptoms at home by making more appropriate use of quick relief medication (37).

Another potential clinical implication of our findings is that routine measurement of adherence to treatment could facilitate clinical management of pediatric asthma by identifying problematic patterns of nonadherence that lead to undertreatment and increased health care utilization and providing targeted behavioral interventions to reduce the high levels of treatment nonadherence (38).

**ACKNOWLEDGMENTS**

The assistance of Jill Goodman, Leigh Josie, Tara Moore, Kristin Barret, and Terri Casey in conducting this study and Meggie Bonner in typing this manuscript is gratefully acknowledged.

**DECLARATION OF INTEREST**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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