A Review of the Effects of Medication Delivery Systems on Treatment Adherence in Children with Asthma

Robert C. Cohn, MD

Department of Pediatrics, MetroHealth Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio

ABSTRACT

Background: A patient's adherence to an appropriate treatment regimen is necessary to minimize morbidity and mortality associated with childhood asthma. Many factors influence the success of treatment adherence.

Objective: The goal of this article was to examine the effect of the mode of medication delivery on the success of treatment adherence in children with asthma.

Methods: Relevant clinical studies were identified through a MEDLINE search of articles published from 1966 to 2002, using the search terms *adherence, aerosol, asthma, children, compliance, dry powder inhaler, metered-dose inhaler, nebulizer, and pediatric*.

Results: A relationship seems to exist between treatment adherence and the type of medication delivery system used in childhood asthma. The highest rates of adherence appear to be associated with oral medications.

Conclusions: Clinicians should consider the mode of medication delivery as 1 factor that can influence the success of treatment adherence. (*Curr Ther Res Clin Exp.* 2003;64:34–44) Copyright © 2003 Excerpta Medica, Inc.

Key words: asthma, pediatric, children, metered-dose inhaler, dry powder inhaler, adherence, compliance.

INTRODUCTION

Asthma affects 4 to 5 million children in the United States¹; its prevalence in children has increased 160% in the past 2 decades, and its severity also has increased.¹ Despite improvements in medications used to treat asthma, childhood asthma morbidity and mortality rates have risen.² Between 1979 and 1995, asthma deaths more than doubled in children aged 0 to 14 years.² A high percentage of deaths have occurred in children and adolescents who appeared

to have mild disease and no other significant comorbidities.^{3,4} Although many factors may affect outcome, medications are of no benefit if children cannot or do not adhere to a treatment regimen.^{3,4}

Although the clinicians have 2 options in the delivery of controller medication (oral and inhaled), in no other chronic illness is the choice of medication and medication delivery system as important. As health care providers, we must seriously consider factors such as mode of medication delivery, which may affect treatment adherence, especially in a disease with serious consequences should exacerbations occur.

This article examines the effect of the mode of medication delivery on the success of treatment adherence. Relevant clinical studies were identified through a MEDLINE search of articles published from 1966 to 2002, using the search terms *adherence, aerosol, asthma, children, compliance, dry powder inhaler (DPI), metered-dose inhaler (MDI), nebulizer, and pediatric*.

DRUG DELIVERY

Three inhaler systems are capable of delivering appropriately sized particles to the lower respiratory tract: nebulizers, MDIs, and DPIs. Nebulizers have been used for asthma therapy in pediatrics for many years. With this mode of medication delivery, large doses of a wide range of medication can be delivered to patients of any age, with no special breathing technique required. Unfortunately, nebulizer therapy can be expensive, inconvenient, and time consuming.

MDIs have been a popular delivery system for the treatment of asthma. Inhaled nonsteroidal or corticosteroidal anti-inflammatory agents have been mainstays of therapy to reduce chronic airway inflammation and control symptoms. It is not unusual for patients to have up to 3 MDIs that they need to use on a daily basis. However, to use an MDI correctly, an individual must perform 9 steps correctly (Table I).^{4,5}

Many errors in MDI technique have been described,⁶ with all patients, regardless of age, having the most difficulty coordinating the actuation of the MDI with inhalation. In a study by Larsen et al,⁷ >75% of adults trained in the

Table I. Nine-step technique for use of a metered-dose inhaler.^{4,5}

1. Shake the canister at least 3 times.
2. Hold the canister upright.
3. Exhale to functional residual capacity.
4. Place the mouthpiece correctly.
5. Activate at the start of inhalation.
6. Inhale slowly and deeply.
7. Take only 1 puff with 1 inhalation.
8. Hold breath for at least 5 seconds.
9. Exhale, repeat puffs as directed. Wait 1 minute between puffs.

9-step process made at least 1 error when demonstrating the technique to others. Interiano and Guatupall⁶ showed that many health care providers also were unable to use an MDI correctly.

Spacer devices can improve and simplify inhaler technique by extending the space between the inhaler and the mouth. Larger particles deposit in the spacer, decrease oral deposition, and allow the user to inhale for a longer period of time without the need for coordination of inspiration and MDI activation. The spacer acts as a reservoir. Newer spacers (eg, Aerochamber™ [Forest Pharmaceuticals, Inc., St. Louis, Missouri] and Optichamber™ [Respironics, Inc.®, Newark, New Jersey]) are valved holding chambers that avoid the problems of coordination of activation and can be used reliably during tidal volume breathing.⁸ Two studies^{8,9} have demonstrated that the efficacy of albuterol delivered by MDI with a spacer is comparable to the same drug delivered by nebulizer.

DPIs are effective alternative devices that are not dependent on propellants (eg, chlorofluorocarbons) for drug delivery. Instead, they allow the patient's inspiratory flow to activate and carry drug particles into the lungs.¹⁰ DPIs are appropriate for older children and adults.¹⁰ Most DPIs require that a patient have a peak inspiratory flow rate of 30 to 90 L/min.¹⁰ The DPI is often easier to use than the MDI because hand-breath coordination is not required,¹⁰ but some children may not be able to generate an adequate peak inspiratory flow rate. There is general agreement that the MDI is more difficult to master than is the DPI, and differences exist in patient preference and deposition patterns with different DPIs.¹¹ The multidose DPIs (Diskus® [GlaxoSmithKline, Research Triangle Park, North Carolina] and Turbuhaler® [AstraZeneca Pharmaceuticals LP, Wilmington, Delaware]) have been judged by patients to be easy to operate, and some patients prefer them to an alternative DPI, Diskhaler® (GlaxoSmithKline).^{12,13} However, the taste of the medication, the taste of the propellant, and the impact on the oropharynx are more obvious with the Diskhaler than with an MDI with spacer, or DPIs such as the Turbuhaler. These factors can be reassuring to the patient. In a study¹³ comparing 2 different DPIs—the Diskus and the Turbuhaler—patients preferred the Diskus because they were able to perceive the small amount of lactose in each dose delivered by the Diskus.

ADHERENCE ISSUES

Various studies have demonstrated increased illness, exacerbations, visits to the emergency department, morbidity, and mortality in asthma patients who are noncompliant or nonadherent to their treatment regimens.^{14–19}

The terms *compliance* and *adherence* often are used interchangeably in the medical literature. Although *compliance* has been defined as “the extent to which a person's behavior coincides with medical or health advice,”^{14,20} some authors prefer the term *adherence* because it suggests a more active role of the patient¹⁴; *adherence* implies a voluntary choice by the patient to closely follow a treatment plan, whereas *compliance* implies passive submission to

the prescriber's treatment regimen.¹⁴ For clarity, *adherence* is used to refer to both compliance and adherence in the remainder of this article, except when describing studies in which *compliance* or both terms are used.

Fish and Lung¹⁴ have outlined the many factors associated with nonadherence and have broken them into 4 categories: patient-related factors, disease-related factors, treatment-related factors, and health care professional-related factors. Patients may be nonadherent to asthma therapy because of a lack of knowledge of the disease and treatment. They may be noncompliant because they reject the diagnosis or because of underlying psychopathology. Decreased physical abilities also might limit adherence. Because patients with asthma may have mild or severe symptoms, intermittent or variable problems, and chronic or acute illness, adherence might be affected. Also, health care professionals may fail to educate patients and/or their families effectively.

Treatment factors related to nonadherence in patients with asthma may include cost, prolonged onset of noticeable action of medication, adverse events, frequency of administration, and skills required for administration.^{14,19,21–29} To improve outcome, clinicians need to focus on these factors. Although asthma education is important, it is not always sufficient to increase adherence; clinician–patient communication may be more important. Asking about the frequency of medication use has been shown to improve adherence. Clinicians need to listen to children and their caregivers, taking into consideration their abilities and lifestyles.

Accurate assessment of treatment adherence may be difficult. Although some studies use direct observation or infer compliance by measuring drug concentrations in blood, urine, or saliva,³⁰ many studies rely on self-reporting, which is the most common means of indirect measurement. Tablet counts and canister weights are other, less reliable indirect measurements. Electronic monitors allow researchers to study patterns of drug use and adherence. Electronic monitors and electronic adherence devices provide much more accurate objective documentation of medication use than do the indirect measurement methods by recording date and time of medication use.^{23,31,32} These devices, such as the MDILog™ (WestMed, Inc., Denver, Colorado), most often have been used with MDIs to assist in measuring and improving compliance.¹⁰ The MDILog fits over most MDIs. In addition to recovering date and time of medication use, the MDILog can be used to determine whether the patient shook the device before inhaling and to assess inhalation technique.¹⁰ Data can be downloaded electronically and reviewed at will. In addition to serving as a reporting tool for compliance, the MDILog can be used to give patients feedback about their actual inhaler use, improving technique and compliance.¹⁰ The validity and reliability of the MDILog have been well characterized.³³ In a study³³ assessing MDILog features, clocking was accurate in 100% of cases. Agreement of late and multiple actuations between the MDILog and paper records from reliable observers was at least 98%.

Adherence to Oral Therapy

Study results^{16,30,34–39} are shown in Table II. Some of these studies have been summarized previously.⁴⁰ For the most part, patients and their families prefer the oral route of administration for asthma medications. In a study⁴¹ conducted at centers around the world, asthmatic adolescents, given the choice, preferred zafirlukast by a ratio of 2.6:1 over inhaled beclomethasone dipropionate. Likewise, in a study⁴² of parental attitudes toward the use of inhaled therapy in children with chronic asthma, 66% of parents surveyed were concerned about inhaled therapy. The most common concerns were medication side effects (91%), inhaler dependency (86%), cost of the inhaler (34%), and difficulty in using the inhaler (15%). Most parents perceived the oral route to be superior to the inhaled route and preferred the oral route for control of chronic asthma. Children of these parents were twice as likely to miss >25% of prescribed doses of inhaled corticosteroids as were the children of parents who did not perceive the oral route of treatment to be superior to inhaled therapy. Parental concerns about inhaled therapy appear to negatively affect treatment adherence.

Bukstein et al⁴³ examined the association between choice of first-line asthma control therapy and health care resource utilization and expenditures in adult patients with mild asthma. Treatment adherence, as measured by the number of prescriptions filled per year, was better in patients prescribed oral montelukast sodium versus inhaled fluticasone propionate (5.1 vs 3.1). Patients receiving montelukast used significantly less rescue medication, as measured by fewer

Table II. Summary of adherence/compliance studies with controller medication.

Study	Delivery Systems/Medication	Patient Type	Adherence/Compliance Rate, %
Kelloway et al ³⁴	Oral theophylline	Adolescents and adults	79 (34) (compliance)*
Kelloway et al ³⁴	MDI, cromolyn, corticosteroid	Adolescents	44 (34) (compliance)*
		Adults	54 (43) (compliance)*
Chung and Naya ³⁰	Oral zafirlukast	Adults	89 (compliance); 71 (adherence)
Celano et al ³⁵	MDI, corticosteroid, cromolyn	Children	44 (adherence)
Milgrom et al ¹⁶	MDI, corticosteroid	Children	58.4 (compliance)
Apter et al ³⁶	MDI, corticosteroid	Adults	63 (38) (adherence)*
Mann et al ³⁷	MDI, corticosteroid	Adults	67 (36) (compliance)*
Jonasson et al ³⁸	DPI, budesonide	Children	76.9 (compliance at 3 mo); 54.2 (compliance at 9 mo); 48.8 (compliance at 27 mo)
Bosley et al ³⁹	DPI, budesonide	Adults	60–70 (compliance)

MDI = metered-dose inhaler; DPI = dry powder inhaler.

*Value is expressed as mean (SD).

prescriptions of inhaled beta-agonists filled per year, than did patients receiving fluticasone (0.19 vs 0.66; $P = 0.03$).

Kelloway et al³⁴ compared treatment compliance with prescribed oral and inhaled asthma medications, using medical records data and pharmacy claims data from 119 patients who had prescriptions for oral theophylline and inhaled corticosteroids and/or cromolyn. Of these patients, 105 were aged 18 to 65 years (mean age, 42 years), and the remainder were aged 12 to 17 years. The population was predominately white and upper middle class. The authors noted the following mean (SD) compliance rates: theophylline, 79% (34%); inhaled corticosteroids, 54% (43%), and cromolyn, 44% (34%). When stratified for age, patients aged 12 to 17 years had the following compliance rates: theophylline, 73%; inhaled corticosteroids, 30%; and cromolyn, 28%. In the group aged 18 to 65 years, the theophylline compliance rate was 80%, and the inhaled corticosteroid compliance rate was 57%. No significant difference was found in compliance rates for oral theophylline versus inhaled corticosteroid dosing frequency (twice daily or 3 times daily).

Chung and Naya³⁰ were the first to use an electronic monitoring device to study adherence and compliance to an oral twice-daily zafirlukast treatment regimen. Fifty-seven patients with stable asthma, aged 18 to 55 years, were given a 12-week regimen of zafirlukast 20 mg twice daily. The Track Cap^{TM} electronic monitoring device (APREX Corp., Fremont, California) recorded the date and time when patients removed and replaced the medication bottle cap. *Compliance* was defined as the number of Track Cap events per number of prescribed tablets, and the difference between the number of tablets dispensed and number returned per number prescribed. *Adherence* was defined as the number of days with 2 Track Cap events at least 8 hours apart per the total number of days' dosing. The median compliance rate was 89%, and the median adherence rate, 71%, suggesting that compliance with and adherence to asthma treatment when using oral twice-daily zafirlukast was very good.

Adherence to Inhaled Therapy

Surprisingly, few data examining patient adherence to nebulizer therapy are available in the medical literature. A MEDLINE search conducted by this author of the years 1966 to 2002, using the search terms *adherence*, *aerosol*, *asthma*, *children*, *compliance*, *dry powder inhaler*, *metered-dose inhaler*, *nebulizer*, and *pediatric*, revealed no articles examining compliance rates with nebulizer treatment in children or adults with asthma.

Metered-Dose Inhalers

Most studies have documented relatively poor adherence to controller medications delivered by MDIs. Celano et al³⁵ investigated the adherence to MDI treatment in low-income, urban, black children with asthma. Adherence to treatment with anti-inflammatory agents was estimated by determining a ratio of the number of puffs used over the study period to the number of puffs

prescribed. The number of puffs was estimated using canister weights, if available, and/or the number of canisters provided according to pharmacy records. The estimated adherence rate for 34 children ranged from 0% to 100% (mean, 44%). Data from this study also suggested that when canister weight was used for verification, many children overestimated their adherence.

In a study by Milgrom et al,¹⁶ children with asthma were recruited for the assessment of compliance with MDI regimens of corticosteroids and beta-agonists. Medication use was reported using diary-card entries and by electronic monitoring using the MDI Chronolog (Forefront Technologies, Inc., Lakewood, Colorado). The median rate of inhaled beta-agonist use reported by patients in their diaries was 78.2%, whereas the median rate of actual use determined by electronic monitoring was 62.1%. The discrepancy between reported and actual use of inhaled corticosteroids was much greater. The median rate of use of inhaled corticosteroids reported by patients in their diaries was 95.4%, whereas the median actual rate of use was only 58.4%. The median compliance rate with inhaled corticosteroids was 13.7% for children who experienced asthma exacerbations sufficient to require a burst of oral corticosteroids. For children who did not require oral rescue corticosteroid treatment, the compliance rate was 68.2%. In a separate study of 50 adults with moderate to severe asthma, Apter et al³⁶ found similar results. The mean (SD) adherence rate was 63% (38%) for twice-daily dosing of inhaled corticosteroids administered by MDI.

Furthermore, adherence to a regimen of corticosteroids by MDI is not likely to improve during periods of increased asthma severity. Mann et al³⁷ recorded mean daily compliance (number of inhalations/number of prescribed inhalations) and underuse and overuse of beclomethasone delivered by MDI with chronology in 10 adults. Mean (SD) daily compliance was 67% (36%). Underuse was observed on 69% of days and overuse on 11% of days.

Despite relatively poor adherence to inhaled corticosteroid therapy, establishing individualized, home-based interventions (eg, goal setting, monitoring, feedback, reinforcement, targeting known barriers to individualize a family-based asthma action plan) significantly enhanced adherence to daily use of inhaled corticosteroids in children with asthma living in inner-city Baltimore.⁴⁴ Electronic monitors were installed on each child's MDI to provide immediate feedback on medication adherence to the families and to validate medication use. At baseline, only 28.6% were using medications as prescribed. Within 4 weeks, 54.1% of children were using their MDIs. The number of children with no medication use decreased from 28.3% at baseline to 15.1%.

Dry Powder Inhalers

Adherence data are more limited for DPIs than for MDIs. Interestingly, results are not much different from those described for MDIs.

Jonasson et al³⁸ measured asthma treatment adherence in children with mild asthma receiving long-term preventive treatment with budesonide delivered by Turbuhaler. Children receiving budesonide had a 76.9% measured compliance

rate at 3 months, 54.2% at 9 months, and 48.8% at 27 months of therapy. Measured treatment compliance was significantly higher for evening medication compared with morning medication for all intervals examined after 9 months. The investigators concluded that treatment adherence and compliance diminish over time and must, therefore, be monitored closely.

Adherence does not appear to be greater when a beta-agonist and a corticosteroid are combined in a DPI. Bosley et al³⁹ compared compliance with inhaled budesonide, terbutaline, and the 2 dry combinations in the Turbuhaler. In this open-label, multicenter study, 102 asthmatic patients were given the 2 drugs in separate Turbuhalers or combined in one. When 2 separate Turbuhalers were used, the average compliance rate was 60% to 70%, and treatment was taken as prescribed on 30% to 40% of study days over a 12-week period. Overuse occurred on <10% of days. Compliance was not significantly different in patients who used the combined inhalers.

DISCUSSION AND CONCLUSIONS

Asthma treatment–adherence issues seem to be no different for adults than for children. Representative studies suggest higher adherence rates with oral medications than with inhaled medications. In addition, the following factors appear to be important in improving adherence to treatment with inhaled corticosteroids³⁶: (1) improved communication between the provider, patient, and caregiver, emphasizing the importance of inhaled corticosteroids for proper long-term control of the patient's asthma; (2) a treatment regimen that is as simple as possible, with the least number of daily doses and inhalations; and (3) an inhaler device that is easy to learn and use.

Therapy should be kept as simple as possible. Clinicians should determine patients' priorities and abilities. If possible, clinicians should select the medication delivery method that will maximize adherence. A written action plan always should be given to patients and their families. In addition, inhaler technique should be taught to families and peers, and their support should be enlisted to ensure adherence success.

These issues have been suggested to improve treatment outcome. Poor inhaler technique is a major cause of underdosing and nonadherence.³⁸ As Chapman et al⁴⁵ have pointed out, when focusing on adherence, it is important to keep sight of clinical outcome. It is better to achieve asthma control with medication being taken less often than prescribed than to achieve perfect adherence with medication that fails to control the disease.^{12,38}

Additional studies should be conducted in children with asthma to assess their treatment adherence, response to therapy, exacerbations, complications of therapy, and outcomes.

ACKNOWLEDGMENTS

The author thanks Wendy Musarra and James Martin for their assistance with manuscript preparation, and the Edwin D. Northrup II Foundation, Cleveland,

Ohio, for their financial support of the Pediatric Asthma Compliance and Technique Clinic at MetroHealth Medical Center.

REFERENCES

1. Grant EN, Wagner R, Weiss KB. Observations on emerging patterns of asthma in our society. *J Allergy Clin Immunol*. 1999;104:S1–S9.
2. Asthma mortality and hospitalization among children and young adults—United States, 1980–1993. *MMWR Morb Mortal Wkly Rep*. 1996;45:350–353.
3. Weiss KB, Gergen PJ, Wagener DK. Breathing better or wheezing worse? The changing epidemiology of asthma morbidity and mortality. *Annu Rev Public Health*. 1993;14:491–513.
4. Foland AP, Stern T, Ramacciotti T, et al. Improvement of metered-dose inhaler administration technique: The effect of training sessions at a specialized pediatric asthma compliance and technique clinic. *Curr Ther Res Clin Exp*. 2002;63:142–147.
5. Cohn RC, Brouhard BH. Technical skills in chronically ill children. *Clin Pediatr (Phila)*. 2000;39:347–349.
6. Interiano B, Guatupall KK. Meter dose inhalers: Do health care providers know what to teach? *Arch Intern Med*. 1993;153:81–85.
7. Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered dose inhaler technique in 501 patients. *J Asthma*. 1994;31:193–199.
8. Amirav I, Newhouse MT. Metered-dose inhaler accessory devices in acute asthma: Efficacy and comparison with nebulizers: A literature review. *Arch Pediatr Adolesc Med*. 1997;151:876–882.
9. Schuh S, Johnson DW, Stephens D, et al. Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebulizer in children with mild acute asthma. *J Pediatr*. 1999;135:22–27.
10. Haider D. New millennium technology to help with asthma management. *AARC Times*. 2002;26:34–40.
11. Branco Ferreira M, Santos A, Clode MH, Palma Carlos AG. Turbutest in the training of asthmatic Turbuhaler users. *Allergy*. 1999;54:375–379.
12. Bouler LP, Cowie R, Johnston P, et al, for the Canadian Study Group. Comparison of Diskus inhaler, a new multidose powder inhaler, with Diskhaler inhaler for the delivery of salmeterol to asthmatic patients. *J Asthma*. 1995;32:429–436.
13. Chapman KR, Balter MS, Boulet LP. Handling of the multidose powder inhalers: Diskus versus Turbuhaler in elderly asthmatics. *Am J Respir Crit Care Med*. 1996;153:A61. Abstract.
14. Fish L, Lung CL, for the Antileukotriene Working Group. Adherence to asthma therapy. *Ann Allergy Asthma Immunol*. 2001;86(Suppl 1):24–30.
15. Schmalings KB, Afari N, Blume AW. Predictors of treatment adherence among asthma patients in the emergency department. *J Asthma*. 1998;35:631–636.
16. Milgrom H, Bender B, Ackerson L, et al. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol*. 1996;98:1051–1057.
17. Ordonez GA, Phelan PD, Olinsky A, Robertson CF. Preventable factors in hospital admissions for asthma. *Arch Dis Child*. 1998;78:143–147.
18. Van Ganse E, Hubloue I, Vincken W, et al. Actual use of inhaled corticosteroids and risk of hospitalization: A case control study. *Eur J Clin Pharmacol*. 1997;51:449–454.
19. Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: Is there a solution to the problem? *Ann Allergy Asthma Immunol*. 1997;79:177–185.

20. Conway A. Adherence and compliance in the management of asthma: 1. *Br J Nurs*. 1998;7:1313–1315.
21. Milgrom H, Bender B. Nonadherence to asthma treatment and failure of therapy. *Curr Opin Pediatr*. 1997;9:590–595.
22. Creer TL, Levstek D. Medication compliance and asthma: Overlooking the trees because of the forest. *J Asthma*. 1996;33:203–211.
23. Bender B, Milgrom H, Rand C, Ackerson L. Psychological factors associated with medication nonadherence in asthmatic children. *J Asthma*. 1998;35:347–353.
24. Bosley CM, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. *Eur Respir J*. 1995;8:899–904.
25. Weinstein AG, Faust D. Maintaining theophylline compliance/adherence in severely asthmatic children: The role of psychologic functioning of the child and family. *Ann Allergy Asthma Immunol*. 1997;79:311–318.
26. Gibson NA, Ferguson AE, Aitchison TC, Paton JY. Compliance with inhaled asthma medication in preschool children. *Thorax*. 1995;50:1274–1279.
27. Huss K, Travis P, Huss RW. Adherence issues in clinical practice. *Lippincotts Prim Care Pract*. 1997;1:199–206.
28. Cochrane GM. Compliance and outcomes in patients with asthma. *Drugs*. 1996; 52(Suppl 6):12–19.
29. Schmier JK, Leidy NK. The complexity of treatment adherence in adults with asthma: Challenges and opportunities. *J Asthma*. 1998;35:455–472.
30. Chung KF, Naya I. Compliance with an oral asthma medication: A pilot study using an electronic monitoring device. *Respir Med*. 2000;94:852–858.
31. Wamboldt FS, Bender BG, O'Connor SL, et al. Reliability of the model MC-311 MDI chronolog. *J Allergy Clin Immunol*. 1999;104:53–57.
32. Bender B, Wamboldt FS, O'Connor SL, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Ann Allergy Asthma Immunol*. 2000;85:416–421.
33. Apter AJ, Tor M, Feldman HI. Testing the reliability of old and new features of a new electronic monitor for metered dose inhalers. *Ann Allergy Asthma Immunol*. 2001;86:421–424.
34. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. *Arch Intern Med*. 1994;154:1349–1352.
35. Celano M, Geller RJ, Phillips KM, Ziman R. Treatment adherence among low-income children with asthma. *J Pediatr Psychol*. 1998;23:345–349.
36. 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(6 Pt 1):1810–1817.
37. Mann MC, Eliasson O, Patel K, ZuWallack RL. An evaluation of severity-modulated compliance with Q.I.D. dosing of inhaled beclomethasone. *Chest*. 1992;102:1342–1346.
38. Jonasson G, Carlsen KH, Mowinckel P. Asthma drug adherence in a long term clinical trial. *Arch Dis Child*. 2000;83:330–333.
39. Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaled medication: Does combining beta-agonists with corticosteroids improve compliance? *Eur Respir J*. 1994;7:504–509.
40. Cochrane MG, Bala MV, Downs KE, et al. Inhaled corticosteroids for asthma therapy: Patient compliance, devices, and inhalation technique. *Chest*. 2000;117:542–550.
41. Weinberg EG, Naya I. Treatment preferences of adolescent patients with asthma. *Pediatr Allergy Immunol*. 2000;11:49–55.

42. Chan PW, DeBruyne JA. Parental concern towards the use of inhaled therapy in children with chronic asthma. *Pediatr Int.* 2000;42:547–551.
43. Bukstein DA, Henk HJ, Luskin AT. A comparison of asthma-related expenditures for patients started on montekulast versus fluticasone propionate as monotherapy. *Clin Ther.* 2001;23:1589–1600.
44. Bartlett SJ, Lukk P, Butz A, et al. Enhancing medication adherence among inner-city children with asthma: Results from pilot studies. *J Asthma.* 2002;39:47–54.
45. Chapman KR, Walker L, Cluley S, Fabbri L. Improving patient compliance with asthma therapy. *Respir Med.* 2000;94:2–9.

Address correspondence to:

Robert C. Cohn, MD
Department of Pediatrics
MetroHealth Medical Center
2500 MetroHealth Drive
Cleveland, OH 44109
E-mail: rcohn@metrohealth.org