

Balancing safety and efficacy in the treatment of pediatric asthma

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The treatment of pediatric asthma requires balancing the efficacy and safety of various asthma medications, facilitating patient and family education, and developing a supportive treatment network. The efficacy and safety of the major asthma controllers—cromolyn, long-acting β_2 -agonists, inhaled corticosteroids, and leukotriene receptor antagonists—are well tolerated overall when used appropriately. Cromolyn is used often as first-line therapy in treating pediatric asthma, but the inhaled corticosteroids remain the cornerstone of pediatric asthma control. Long-acting β_2 -agonists are most beneficial when used intermittently or in combination with other asthma medications. The most recent class of drugs, the leukotriene receptor antagonists are effective in controlling asthma and are well tolerated in children as young as 2 years of age. In moderate-to-severe pediatric asthma, combination therapy is often required to achieve optimal asthma control. Leukotriene receptor antagonists combined with inhaled corticosteroids reduce the need for steroid rescue, the rate of serious exacerbations, and the level of inflammation. The treatment of asthma requires the ability to diagnose and treat asthma effectively. In subpopulations with special needs such as very young or inner-city minority children, treating asthma requires a comprehensive approach that includes a supportive patient-physician relationship and the involvement of schools, churches, and neighborhood outreach programs that will identify children with asthma and promote quality care. (*J Allergy Clin Immunol* 2002;109:S560-6.)

Key words: Asthma, pediatric, efficacy, safety, treatment

As the most common and rapidly growing chronic childhood illness, asthma afflicts over 4 million children, 1.3 million younger than 5 years of age and 2.8 million 5 to 14 years of age.¹ Among children, the prevalence of asthma has more than doubled over the past 20 years, underscoring the need for effective early treatment to control this often debilitating and sometimes fatal disease. The development of an effective treatment plan, however, is a process that requires balancing the benefits and risks of a particular asthma intervention. This article will review the efficacy and safety profiles of common controller medications used in treating pediatric asthma and discuss some of the challenges faced in treating this disease in certain pediatric subpopulations, including preschoolers and inner city children.

Abbreviations used

CAMP: Childhood Asthma Management Program
CSS: Churg-Strauss syndrome
EIB: Exercise-induced bronchoconstriction
ICS: Inhaled corticosteroids
LTRAs: Leukotriene receptor antagonists
PEFR: Peak expiratory flow rate

CROMOLYN

The anti-inflammatory agent cromolyn sodium has induced significant long-term benefits in the treatment of asthma. In a 52-week, multicenter study, 397 patients with poorly controlled asthma received cromolyn sodium in addition to ongoing therapy.² During the study, the addition of inhaled cromolyn sodium 4 times daily resulted in significant ($P < .05$) improvements in morning and evening peak expiratory flow rates (PEFR) as well as reductions in asthma symptom scores and exacerbation rates. Findings such as these have helped establish cromolyn sodium as a first-line controller medication for treating chronic asthma. Furthermore, inhaled cromolyn is remarkably well tolerated; over the past 30 years, no important changes have been made to the safety profile of this agent.

LONG-ACTING β_2 -AGONISTS

Inhaled long-acting β_2 -agonist treatment produces bronchodilation, but whether it induces long-term bronchoprotective effects remains controversial. In a multicenter, double-blind, parallel-group study, children between the ages of 4 and 11 years with chronic persistent asthma were randomly assigned to twice-daily inhaled salmeterol (50 μ g) or placebo treatment.³ Twelve-hour postdose pulmonary function assessments conducted after the 12-week treatment period revealed significant improvements in PEFR ($P = .008$) and FEV₁ ($P < .001$) at all time points evaluated with salmeterol treatment when compared with placebo. Also, significant reductions were seen in asthma symptom scores ($P = .006$) and supplemental albuterol use ($P = .004$) with salmeterol treatment. Other investigators have shown that the bronchodilation seen with long-acting β_2 -agonists may decrease over time.

In a long-term (54-week) study, researchers examined the effects of 50 μ g salmeterol or 200 μ g beclomethasone twice daily on pulmonary function and symptoms in 67 children with mild-to-moderate asthma not previously treated with corticosteroids.⁴ Upon completion of the study, mean FEV₁ measurements significantly increased

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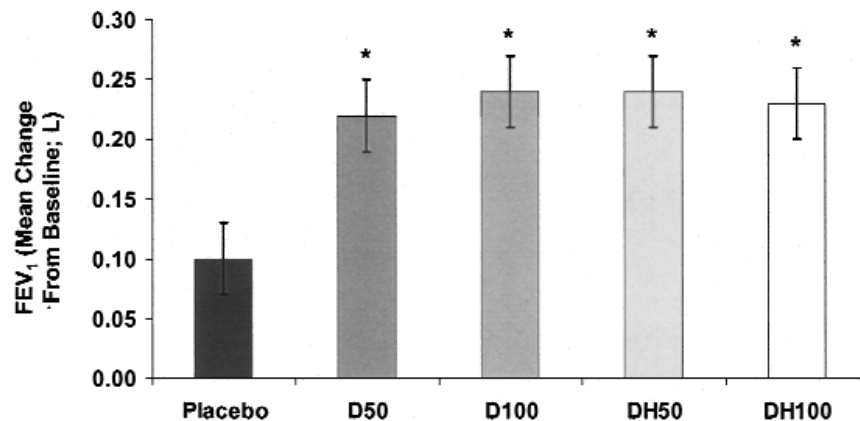


FIG 1. Inhaled corticosteroid efficacy. Compared with placebo, fluticasone (50 or 100 µg twice daily) delivered by either of two easy-to-use, breath-activated, dry powder delivery devices resulted in significant improvement in pulmonary function, as measured by changes in FEV₁ from baseline. D, Diskus; DH, Diskhaler; dosage indicated is µg bid). * $P < .023$ vs placebo at end point. (Adapted from data in Peden et al.⁷)

with beclomethasone treatment ($P < .001$). These measurements, however, decreased slightly with salmeterol treatment, although the decrease was not significant. Moreover, improvements in symptom scores were greater with beclomethasone compared with salmeterol treatment; however, the difference was only significant at some time points. In a similarly designed study, beclomethasone treatment was associated with significantly less airway hyperresponsiveness ($P = .003$), assessed by methacholine challenge, than salmeterol.⁵ Improvements in pulmonary function with salmeterol were less than those seen with beclomethasone and were not sustained over the course of the 12-month evaluation. These data suggest that long-acting β_2 -agonists offer minimum long-term bronchoprotection and are inadequate for use as monotherapy in mild-to-moderate pediatric asthma.

A recent meta-analysis of 30 studies examined the long-acting β_2 -agonists, salmeterol, and formoterol in the control of pediatric asthma.⁶ Single doses were found to produce prolonged (>12 hours) bronchodilation and protection against exercise-induced bronchoconstriction (EIB), but the extent and duration of improvement appeared minimal with regular use. The data also showed that partial tolerance develops with the regular use of long-acting β_2 -agonists as well as cross-tolerance to short-acting β_2 -agonists. In conclusion, this meta-analysis did not support the use of long-acting β_2 -agonists as monotherapy. Long-acting β_2 -agonists are generally safe. Adrenergic adverse effects, such as headaches, tremors, and heart palpitations, usually occur only in sensitive patients and appear to be dose related. Patient education, however, is necessary to prevent over-dosage and to clarify appropriate use.

INHALED CORTICOSTEROIDS

Inhaled corticosteroids (ICS) are the cornerstone of pediatric asthma control. Their benefits in improving and sustaining increases in pulmonary function and in reduc-

ing symptomatology have been clearly demonstrated. Increasingly, ICS are used in treating asthma in young children. The benefits of fluticasone (50 or 100 µg twice daily, administered by two different, easy-to-use, breath-activated, dry powder delivery devices) in 437 children 4 to 11 years of age with persistent asthma were explored in a 12-week, double-blind, parallel-group study.⁷ Compared with placebo, fluticasone delivered by either device resulted in significant ($P \leq .023$) improvements in mean changes in FEV₁ from baseline (Fig 1). Significant improvements were noted in mean PEFR ($P \leq .006$), supplemental albuterol use ($P \leq .002$), and asthma symptom scores ($P \leq .036$). These results demonstrated the benefits of the ICS fluticasone in children as young as 4 years of age, regardless of previous corticosteroid treatment.

A separate 12-week, parallel-group study evaluated the effects of inhaled budesonide once daily (0.25 mg and 1.0 mg) and twice daily (0.25 mg and 0.5 mg) in 480 young children 6 months to 8 years of age with moderate, persistent asthma.⁸ Although all the dose levels of budesonide produced significant improvements in most efficacy measures, FEV₁ measurements increased significantly ($P \leq .05$) only at the 0.5 mg budesonide twice-daily dose level compared with placebo. The results of this study supported the effectiveness of ICS in very young children with moderate asthma and the usefulness of once-daily budesonide dosing as an option in this patient population.

Inhaled corticosteroids are generally well tolerated. Effects such as oral infection and dysphonia are dependent on the mode of delivery; however, with the proper use of a spacer or flow-activated devices, these effects are uncommon. In children, however, the effects of ICS on vertical growth, bone density, and adrenal suppression have been a concern.

A review of published studies on the effects of moderate doses of ICS on vertical growth velocity in children with mild-to-moderate asthma revealed only decreases in linear growth. A meta-analysis of 4 studies with beclomethasone supported the conclusion that there is a significant decrease

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FIG 2. Changes in linear growth velocity with beclomethasone. Meta analysis of inhaled beclomethasone in children with asthma with a fixed-effects model, weighted-mean-difference (*WMD*) in linear growth velocity and 95% CI. Negative values of weighted mean difference represent a reduced linear growth velocity for each respective study. Box areas are proportional to study weights. (Reproduced with permission: *Pediatrics*, Vol. 106, Page E8, Figure 1, Copyright 2000.)

in linear growth using medium-dose beclomethasone (Fig 2).⁹ All 4 trials showed a mean reduction with no 95% CI crossing zero. The studies included in this analysis were less than 54 weeks in duration.

The Childhood Asthma Management Program (CAMP) studied the effect of budesonide on linear growth in mild-to-moderate asthmatic children 5 to 12 years of age.¹⁰ Children were randomly assigned to receive budesonide, nedocromil, or placebo twice daily for 4 to 6 years. Budesonide caused a clear decrease in growth velocity during the first year of the study (Fig 3) that reduced mean height by 1.1 cm less than the mean height in the placebo group (22.7 vs 23.8 cm, $P = .005$). The decreased growth velocity, however, did not continue beyond the first year, and ultimate projected height was not significantly different.

In a separate study reported at the same time, it was concluded that children treated with ICS still attained their target adult height.¹¹ In children treated with budesonide for an average of 9.2 years, their actual adult height appeared to be no different from their calculated target height. The calculation was based in part on parental height. The results of this study may be problematic. First, the control group decreased from 62 to 18 participants, mainly owing to patients requiring inhaled or oral corticosteroid treatment. In addition, it is doubtful that this study was powered so that it could distinguish the 1.1 cm reduced height, as measured in CAMP, because the equation used to compute the target adult height had a large intrinsic variance (95% predicted interval of approximately ± 10 cm).¹² A lack of difference between a widely variant calculated target height and the actual measured adult height may be a weak basis for concluding that children make up the reduced bone growth during the first year of ICS therapy.

LEUKOTRIENE RECEPTOR ANTAGONISTS

The leukotriene receptor antagonists (LTRAs) are the newest controller medication for pediatric asthma. In an 8-week, double-blind, placebo-controlled trial that comprised 336 asthmatic children 6 to 14 years of age, montelukast significantly ($P \leq .05$) improved FEV₁, and reduced as needed β_2 -agonist use ($P = .01$), the rate of exacerbations ($P = .002$), and blood eosinophils ($P = .02$).¹³ During a 6-month open extension of this study, the improvements in FEV₁ with montelukast were maintained and comparable to the FEV₁ obtained with beclomethasone treatment initiated after the 8-week primary study. Sustained compliance with montelukast was far superior to beclomethasone (Fig 4).¹⁴

The clinical experience with LTRAs has been limited, but clinical studies and postmarketing surveillance data continue to confirm the safety of these agents in children with asthma. A placebo-controlled clinical trial with montelukast in 689 children with asthma 2 to 5 years of age underscores the efficacy and safety profile of this agent.¹⁵ In this study, montelukast reduced days with symptoms ($P = .012$), daytime asthma symptom score ($P = .003$), cough ($P = .003$), wheeze ($P = .042$), trouble breathing ($P = .007$), activity limitation ($P = .001$), β_2 -agonist use ($P = .001$), corticosteroid rescues ($P = .008$), blood eosinophils ($P = .034$), and increased days without asthma ($P = .002$). The most common adverse effects are presented in Table I. The adverse experience profile was comparable to placebo, and montelukast was well tolerated. Furthermore, the discontinuation were similar in both groups (3.1% for placebo and 3.5% for montelukast) as well as the laboratory adverse effects (5.4% vs 3.5% for placebo and montelukast, respectively).

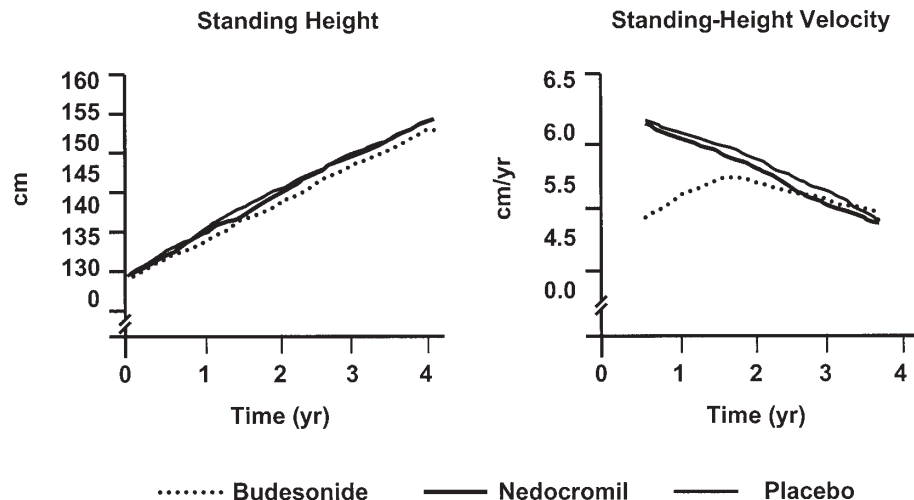


FIG 3. Reduction of growth velocity occurs within the first year of budesonide use. Results from CAMP. Left panel: At the end of the treatment period, the mean increase in height in the budesonide group was 1.1 cm less than the mean increase in the placebo group (22.7 vs 23.8 cm, $P = .005$). Mean height increase was similar in the nedocromil and placebo groups ($P = .65$). Right panel: Difference between budesonide and placebo groups in the rate of growth was evident primarily within the first year of treatment and did not increase later. All groups had similar growth velocity by the end of the treatment period. (Adapted with permission from The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63. Copyright © 2001 Massachusetts Medical Society. All rights reserved.)

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FIG 4. Pediatric open extension study: Pulmonary function. Six-month open-label extension study comparing improved FEV₁ with montelukast to FEV₁ with the ICS beclomethasone. *Number of respective patients providing data at each interval of time. (Adapted from Williams B, Noonan G, Reiss, TF, et al. Long-term asthma control with oral montelukast and inhaled beclomethasone for adults and children 6 years and older. *Clin Exp Allergy* 2001;31:845-54, by permission of Blackwell Science.)

A few cases of Churg-Strauss Syndrome (CSS) were reported in adults receiving LTRA therapy. If left untreated, this rare condition, characterized by necrotizing vasculitis, pulmonary infiltrates, eosinophilia, and possibly cardiomyopathy, can lead to major organ damage and death. This syndrome occurs generally in middle-aged patients and is very rare in children. Only 10 cases worldwide have been reported in children, none of whom were using an LTRA.¹⁶ Asthmatic patients who had CSS generally have had difficult-to-treat asthma, and when their

dose of inhaled or oral corticosteroids is reduced, usually with the use of an alternative controller medication such as an LTRA, the CSS condition is unmasked.¹⁷ The LTRA, then, unmasks the CSS rather than causes it.¹⁸

COMBINATION THERAPIES

For many clinicians, treating pediatric asthma often means treating patients with disease severity typically ranging from moderate to severe. In this setting, combi-

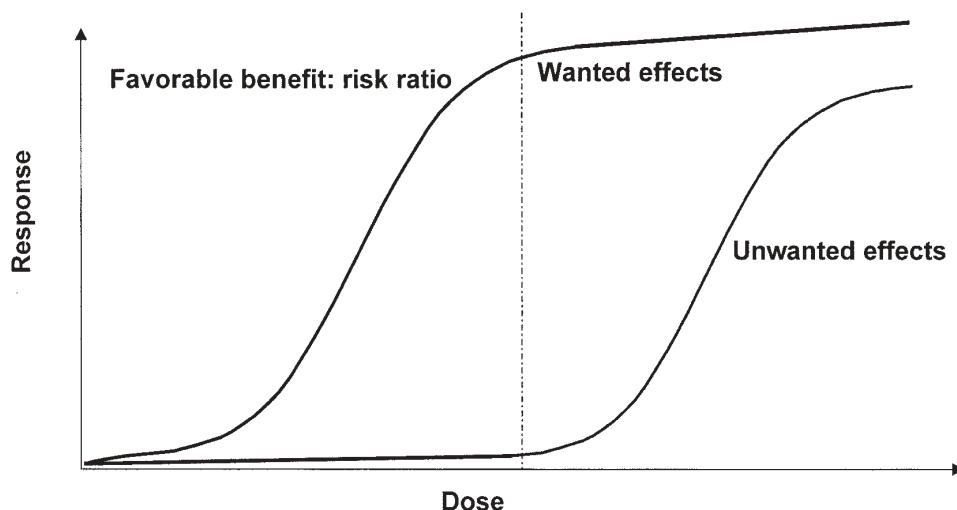


FIG 5. Schematic dose-response curves for wanted and unwanted effects of ICS. The range in which the risk:benefit ratio is favorable is that at which the wanted effects in the lungs increase steeply with dose while the unwanted systemic effects increase gradually. At higher doses, the increase in risk greatly outweighs the slight remaining increase in benefit. (From Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997;52(Suppl 39):1-34. © 1997 Munksgaard International Publishers Ltd. Copenhagen, Denmark.)

nation therapy is often required to achieve adequate control. The benefits of combination therapy in asthma are supported by several studies. In a multicenter study, montelukast (10 mg daily) given to adults permitted a significant ($P = .046$) reduction in concomitant ICS use (47%) compared with placebo (30%), and fewer patients ($P = .01$) receiving montelukast (16%) discontinued the study because of rescue medication failure (placebo treatment was 30%).¹⁹ Another study showed that exhaled levels of nitric oxide, a marker of inflammation, were significantly ($P = .02$) reduced by the addition of montelukast (5 mg once daily) in asthmatic children aged 6 to 15 years receiving a constant dose of ICS as regular therapy.²⁰ These results demonstrated that the addition of an LTRA provided additional anti-inflammatory effects in asthmatic patients already receiving ICS therapy.

Because of a possible risk of masking ongoing inflammation, combining a long-acting β_2 -agonist with ICS is a controversial step in asthma treatment. A recent double-blind, 12-week study in asthmatic patients treated with ongoing ICS and randomly assigned to supplementary treatment with salmeterol, fluticasone, or placebo showed, however, no evidence of airway inflammation reduction associated with the addition of salmeterol therapy.²¹ Bronchial biopsy specimens revealed a decrease in EG-1⁺ eosinophils in the lamina propria after salmeterol but not after fluticasone treatment. This last result suggests that salmeterol may have a potential anti-inflammatory effect, although the significance of this remained unclear.

MAKING APPROPRIATE TREATMENT DECISIONS

When making a decision to treat with a specific drug, the physician has to consider 2 essential parameters: the

efficacy and effectiveness of the drug. The efficacy is the "easiest" to assess because clinical trials give answers on how, under controlled conditions, the drug benefits the patient and adverse effects are carefully observed. In contrast, the effectiveness is a more complex parameter to evaluate. It additionally considers the patient's adherence to the treatment regimen. Effectiveness is the product of efficacy and adherence and ultimately determines the true benefit of the drug outside a clinical trial setting ("real world"). When choosing a treatment, the physician must also consider if it adequately treats the severity of the disease without the risks outweighing the benefits. The range in which the risk: benefit ratio is favorable is that range in which the desired effects in the lungs increase steeply with the dose while the unwanted systemic effects remain low or only slightly increase. At higher doses, the increase in risk may outweigh the slight remaining increase in benefit (Fig 5).²²

Once asthma is diagnosed, the treatment plan for asthmatic children typically reflects the needs of the patients and the severity of disease. In mild asthma, which is often underdiagnosed and undertreated, there is a clear need for early and effective anti-inflammatory therapy. Because of their convenience, effectiveness, and tolerability in young children, LTRAs are certainly one option for initial therapy in these patients. In moderate asthma, however, optimum treatment usually requires combination therapy, such as that provided with an LTRA and low-to-moderate doses of ICS. The purpose of a combination of therapy is to provide added, or synergistic, anti-inflammatory effects (control), while minimizing the ICS dose and the adverse effects associated with it. In severe asthma, early, aggressive therapy is needed to gain rapid control of the disease; the use of high doses of ICS usually accomplishes this. Once asthma control is achieved

and maintained, dosing should be adjusted downward to achieve the minimum effective dose and the least complex dosing regimen. Again, LTRAs may be instrumental in this adjustment because of the synergistic anti-inflammatory effects of these agents.

TREATING ASTHMA IN SUBPOPULATIONS

Preschool-aged children

In preschool-aged children, differentially diagnosing asthma from other respiratory disorders can be particularly challenging. Many young children may contract respiratory diseases, including viral infections that produce wheezing symptoms similar to those seen in asthma. Furthermore, measuring airway function in young children with the use of conventional spirometry is generally impractical or unreliable. As an alternative, forced impulse oscillometry is a simple, reliable, and easy measurement of pulmonary function, which can be used in children as young as 3 years of age. This requires a full-time respiratory therapist and may not be cost-effective in all practice settings.

In pediatric asthma, the perceived risks of therapy, such as even transient growth suppression associated with ICS, and the use of often cumbersome delivery devices discourage adherence and undermine the potential effectiveness of these therapies in the very group in whom asthma intervention can provide the most benefit. In young children with mild asthma, ease of administration, including the use of orally administered agents such as LTRAs, and a high comfort level with the medication are characteristics of treatment that can promote adherence and improve outcomes. Additionally, effective and ongoing care giver and patient education programs are essential to sustaining adherence in young children.

Children in inner cities

The treatment of asthma among minorities living in inner cities poses a series of unique challenges. This population displays excessive asthma morbidity and mortality rates. In Chicago, during the period from 1968 to 1991, asthma mortality rates remained stable for white inner city residents but increased by an alarming 337% among black residents ($P < .001$).²³ Inner city minority children have higher rates of emergency department utilization, and hospitalizations as the result of asthma, and asthma mortality rates have been consistently higher in such children in comparison with other racial groups since the mid-1980s.²⁴⁻²⁶ In New York City, hospitalization and mortality rates are 3 to 5.5 times higher among black and Hispanic persons than among white persons.²⁷

Not only are asthma prevalence and severity rates higher among inner city minority populations, but the failure to provide quality treatment of asthma care in these populations is substantial. A multicenter study that included 8 sites in 7 inner city metropolitan areas surveyed the nature and extent of medication used among 1376 asthmatic children 4 to 9 years of age.²⁸ Among all the asthmatic children, 16% did not use any form of β_2 -

TABLE I. Frequency of most common clinical adverse effects in children 2 to 5 years old

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agonist and more than 51.2% of the patients with mild asthma did not use either an oral or inhaled β_2 -agonist. Similarly, among severely asthmatic patients, only 47.5% were using an ICS or cromolyn as a preventative, anti-inflammatory treatment. Only 52.8% of the children used a spacer device with their prescribed metered-dose inhaler, and only 21.2% of all the children over the age of 6 years were prescribed a peak flowmeter to regularly monitor their airway function. These data show that among inner city children, inadequate asthma treatment is a barrier to effective asthma control.

In a separate study that evaluated treatment practices among 508 inner city children with asthma, 31% of the children were taking theophylline alone or in combination with a β_2 -agonist.²⁹ Only 11% used anti-inflammatory medication, and 20% had no prescription for asthma medication or took an over-the-counter product. For the children who were treated, older medications such as theophylline were used more commonly than were newer anti-inflammatory agents.

Even though indoor and outdoor allergen exposure, socioeconomic factors, and poor education certainly play some role in the increase in asthma prevalence and the higher asthma morbidity and mortality rates among inner city minorities, some evidence exists for a genetic predisposition as well. Racial differences in asthma were explored in a study that included 569 black and white children 6 to 8 years of age.³⁰ The prevalence of physician-diagnosed asthma was 10% in both groups. Black children, however, were more reactive to methacholine challenge, despite adjustment for sex, age, parental education, parental smoking, and maternal smoking during pregnancy. In addition, total serum IgE was significantly ($P = .001$) higher in black children compared with white American children. Remarkably, this study included a preponderance of middle-class subjects in both groups. These data suggest that black children may be predisposed to potentially more severe asthma.

TREATMENT PLAN

When used appropriately, asthma medications can achieve a satisfactory balance of safety and efficacy for most patients. In children, however, the ability to sustain

proper use and patient adherence to a prescribed treatment regimen remains a barrier to effective treatment, even with the use of convenient oral asthma medications. Adequate treatment in the pediatric setting requires a supportive network that includes not only the physician and other health care professionals, but, for certain pediatric populations, community involvement as well.

Physicians who develop a written treatment plan in coordination with the patient and care givers at the initial contact demonstrate concern and encourage patients and care givers to take responsibility for the success of the treatment. Furthermore, establishing and scheduling follow-up visits at the initial contact and confirming those visits before the scheduled appointment increases the likelihood for continuous patient contact. On subsequent visits, the action plan can be reinforced and adherence monitored. Ideally, a clinician should be available by telephone at any time to address a patient's questions about exacerbations or other asthma-related emergencies.

Some pediatric subpopulations, particularly inner city children and very young children under the age of 5 years, require a more extensive level of social support. To increase asthma recognition and diagnosis in these groups, community outreach programs can provide educational seminars at neighborhood churches, schools, or other institutions of importance within a given community. Once a child is diagnosed with asthma, treatment plans should be developed and implemented quickly, but ensuring consistent adherence in many subpopulations can require broad-based community involvement. For instance, schools and day care centers could monitor asthma symptoms and dispense prescribed medications on schedule, improving adherence and outcomes. Achieving a favorable balance of safety and efficacy in pediatric asthma requires a network of support so that medications will be used appropriately and effectively.

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