

Asthma from the perspective of the patient

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Background: The published literature is lacking in data on the frequency and severity of medication side effects in the general asthma population.

Methods: Questionnaires regarding asthma severity, treatment, and medication side effects were answered by 1230 and 604 pediatric and adult asthmatics, respectively, 70% to 75% of whom were consulting a specialist.

Results: Most respondents (58%-79%) reported unwanted side effects from their bronchodilators, most of which had been racemic albuterol prescribed in either generic or name brand form. Side effects were most common in nebulizer users of all ages and in pediatric patients using oral medications. The most common troublesome side effects were jitteriness (58%), restlessness (57%), tachycardia (56%) and cough (56%) in the pediatric patients and tachycardia (64%), jitteriness (60%), shaky hands (43%), and restlessness (42%) in the adult respondents. Most patients had spoken to their physicians about their side effects, and the most common response was to change brands within the same class of medication, adjust the dose, or advise the patients to tolerate the side effects because the medications were necessary and side effects were to be expected. Fewer than 4% of all respondents viewed their physicians as "caring/sympathetic/willing to listen/discuss their bronchodilator side effects." Twenty-five to thirty percent of patients had reduced their bronchodilator dose on their own, and 14% to 24% had skipped doses to avoid unwanted side effects. Hospitalizations were infrequent and were most commonly seen in the nebulizer users, who were also rated by their physicians as more likely to have severe asthma. Other markers of asthma control (such as emergency room visits, unscheduled doctor visits, and being sent home from school/work for asthma symptoms) were not only common in the nebulizer user group but also in children who used oral medications. This group was more likely to have been classified by their physicians as having mild asthma, suggesting perhaps a need for more intensive asthma education in this group.

Conclusion: Medication side effects are common in individuals with asthma and are most often ascribed by the patients to their bronchodilators. There is a need for new, rapid-acting bronchodilators with fewer side effects. (*J Allergy Clin Immunol* 1999;103:S47-52.)

Key words: Asthma, side effects, medications, β -agonists, nebulizer, patient satisfaction

Physicians are trained to systematically evaluate the risks and benefits of all available treatment modalities

Abbreviation used

MDI: Metered dose inhaler

before devising optimum treatment plans for their patients. Those physicians treating patients with asthma may choose a rapidly acting bronchodilator for symptom relief and, in the case of persistent asthma, one or more additional medications (such as inhaled corticosteroids, leukotriene modifiers, methylxanthines, or long-acting bronchodilators). The expansion of our knowledge about the pathophysiology of asthma, coupled with the development of improved pharmaceuticals with delivery systems designed to diminish systemic side effects, has led to highly effective therapies, with resultant improvements in quality of life and what was thought to be minimal side effects.¹⁻³

Recently, however, a disturbing series of papers has been published that suggest that inhaled corticosteroids may have clinically important side effects that were previously under recognized, such as an increased incidence of glaucoma and cataracts in elderly patients and a decreased growth velocity in children.⁴⁻⁶ These data have prompted the Food and Drug Administration to require warnings about potential growth effects in the labeling of all inhaled corticosteroids. Moreover, leukotriene modifiers have been associated with numerous reports of newly diagnosed Churg Strauss syndrome. Although many individuals believe that these reports represent an "uncovering phenomenon," the possibility of a causal relationship should not be over-looked.⁷

Some asthma medications have short-term, reversible side effects that, though annoying for the patients, are less likely to cause long-term or permanent untoward effects. Well-known examples include the inattentiveness and hyperactivity induced by methylxanthines in susceptible children.⁸ These, and other adverse effects, caused methylxanthines to fall out of favor over the last decade or so. However, racemic B₂ agonists, the most commonly prescribed class of asthma medications, also causes a number of reversible side effects that may be disturbing to patients. Perhaps because of the lack of alternatives, physicians have tended to diminish the importance of these side effects. A recent survey of patients with asthma carried out by the Allergy & Asthma Network/Mothers of Asthmatics, Inc on their members suggests that individuals with asthma are disturbed more by quality-of-life issues and medication side effects than clinicians may be aware.

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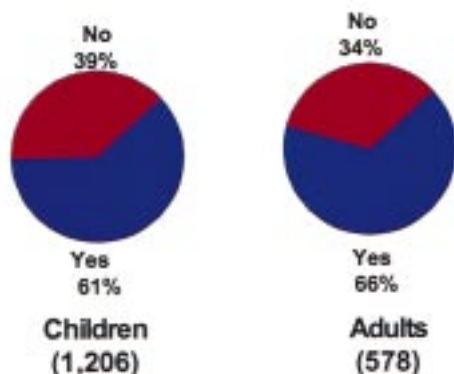


FIG 1. The proportion of children (left) and adults (right) who reported experiencing unwanted side effects from their asthma medications.

PATIENT AND PHYSICIAN CHARACTERISTICS

Twenty-three-page questionnaires were mailed to 4536 members of the Allergy & Asthma Network/Mothers of Asthmatics, 1528 of whom returned completed questionnaires (34%). The child-asthma and adult-asthma questions were answered by 1230 and 604 respondents, respectively. Statistics (*t* tests and Cochran-Mantel-Haenszel tests) were calculated with SAS. (Statistical Analysis Software, Cary, N.C.)

Most of the respondents were cared for by a specialist; 47% of the adults and 57% of the children were being treated by an allergist; 26% of the adults and 20% of the children were consulting a pulmonologist. Children were far more likely than adults to have received a written asthma management plan (65% vs 39%). Allergists and pulmonologists who were treating children were each twice as likely to have provided a written asthma management plan compared with pediatricians, who were about 50% more likely to have provided a management plan as compared with the family practitioner. In contrast, allergists and pulmonologists were one-half as likely to provide written management plans to their adult patients compared with their pediatric patients but were each about 3 times as likely to have provided a written asthma management plan compared with either the internist or the family practitioner.

MEDICATIONS USED BY CHILDREN

Ninety-nine percent of the pediatric respondents reported using a bronchodilator, with 72% reporting use of generic racemic albuterol, 31% receiving Proventil, 25% receiving Ventolin, 8% receiving Proventil-HFA, 16% receiving Serevent, and 5% receiving pirbuterol (Maxair). One percent of respondents reported using one or more alternative bronchodilators, including over-the-counter products. Most of the children (70%) had used nebulized bronchodilators; 79% of the children had received bronchodilators with metered-dose inhalers (MDIs), and 9% of the children had received oral bron-

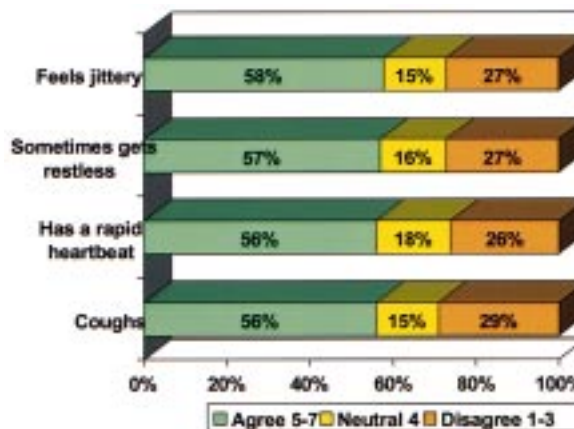


FIG 2. The answers received by pediatric respondents when asked about medication side effects that could be ascribed to their bronchodilators. Possible responses were on a 1 to 7 scale, with 1 representing strongly disagree, and 7 representing strongly agree. The side effects listed are the 4 most common side effects reported in the pediatric group.

chodilators. Of the nonnebulizer users, 14% took oral bronchodilators (4% of all pediatric respondents) and 94% used bronchodilators delivered by MDI (27% of all respondents). The nebulizer users (mean age, 8 years 5 months) tended to have more severe asthma, as classified by the physicians ($P < .05$); however, there were no differences in asthma classification by physicians within the nonnebulizer group between the MDI users (mean age, 10 years 1 month) and the oral medication users (mean age, 10 years 1 month). The nebulizer user group was more likely to have received anti-inflammatory medications (98%) compared with the nonnebulizer group (88%; $P < .05$). There was some cross-over between the MDI and oral medication groups, because some respondents received both forms of medication. For the purposes of this paper, the oral group consisted of those respondents who did not use a nebulizer and who received any oral medication. The MDI group consisted of respondents who did not use a nebulizer but who did use an MDI. Those respondents who used both oral medications and MDI, but no nebulizer, were counted in both groups.

MEDICATION SIDE EFFECTS IN CHILDREN

Medication side effects were reported by the parents of most of the children (63%, 57%, and 79% of nebulizer, MDI, and oral medication users, respectively), with a greater proportion of oral medication users reporting unwanted side effects (Fig 1; $P < .05$). Only 13% to 14% of those children experiencing side effects in each group felt the untoward effects to be strictly the result of their anti-inflammatory medication. The most common bronchodilator-associated side effects reported were jitteriness (58%), restlessness (57%), tachycardia (56%), and cough (56%; Fig 2). All 4 of these untoward effects were observed more frequently in the nebulizer user and oral medication groups as compared with the MDI group (P

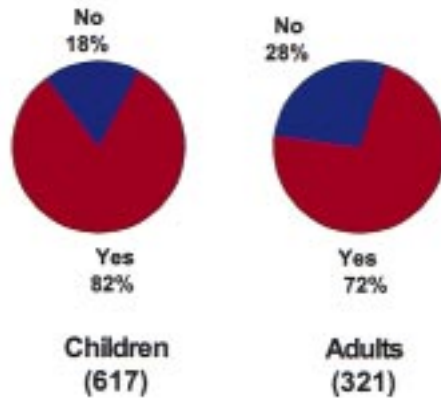


FIG 3. Proportions of children (left) and adults (right) who had spoken to their physicians about medication side effects.

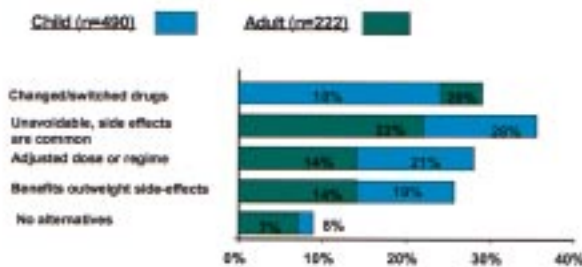


FIG 4. The most common physician responses to complaints about medication side effects in children (left) and adults (right).

< .05 for nebulizer vs nonnebulizer). A high proportion of parents said that their children had “too much energy after taking bronchodilators” (46% of nebulizer users, 30% of MDI users, and 39% of oral medication users; $P < .05$ for nebulizer vs nonnebulizer users). A similar number complained about shaky hands (43%, 38%, and 45% of nebulizer, MDI, and oral medication users, respectively) and difficulty falling asleep (43%, 35%, and 49% of nebulizer, MDI, and oral medication users, respectively, with MDI users having significantly less difficulty than nebulizer or oral medication users; $P < .05$ for nebulizer vs nonnebulizer). Thus although many physicians tend to believe that bronchodilator side effects are mild and only experienced by a few patients, these data suggest quite the opposite (ie, most children receiving bronchodilators, especially by the oral route, experience significant side effects).

Most of the parents (whose children had medication side effects) had discussed the issue of medication side effects with their child’s physician (83%, 80%, and 87% of nebulizer users, MDI users, and oral medication users, respectively; Fig 3). The most common physician responses were that side effects were to be expected and that the benefits outweighed the risk. In only 16% to 24% of the time were any adjustments made to the dose or frequency of dosing or to the product (usually a different brand of the same product was prescribed; Fig 4). Physi-

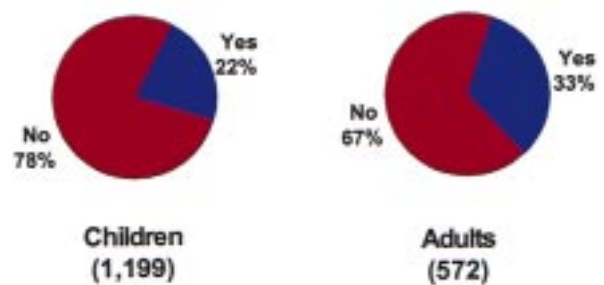


FIG 5. The proportion of respondents who had reduced the dosage of bronchodilators to reduce side effects. Pediatric and adult respondents are depicted on the left and right, respectively.

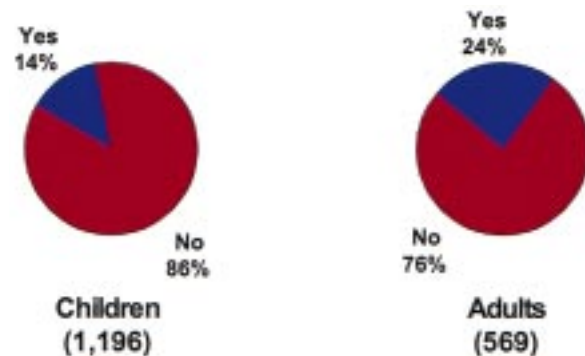


FIG 6. The proportion of respondents who had skipped a dose of bronchodilators to reduce side effects. Pediatric and adult respondents are depicted on the left and right, respectively.

cians were not viewed as caring, sympathetic, willing to listen, or willing to discuss the problem (3%, 3%, and 12% of nebulizer, MDI, and oral medication prescribers, respectively, stated that their physicians were caring/sympathetic). For the parents who did not discuss their concerns with their child’s doctor, the most common reason was the belief that there were no alternatives. Only 10% to 17% failed to discuss the problem because they were already aware of the potential medication side effects. The bronchodilator side effects were considered severe enough to induce 23% of parents to reduce their child’s bronchodilator dose (Fig 5) and 14% of parents to skip giving doses without instructions from their physician (Fig 6). These data illustrate the need to develop better bronchodilators with fewer unwanted side effects but also underscore the importance of physicians maintaining a nurturing bedside manner, especially in the face of limited therapeutic options.

MARKERS OF ASTHMA CONTROL IN CHILDREN

Children in all 3 groups displayed a similar seasonal pattern, reporting significantly fewer asthma exacerbations in the summer months than in the fall, winter, and spring months. Indeed, 30% and 31% of the children reported zero or one asthma exacerbation per month in

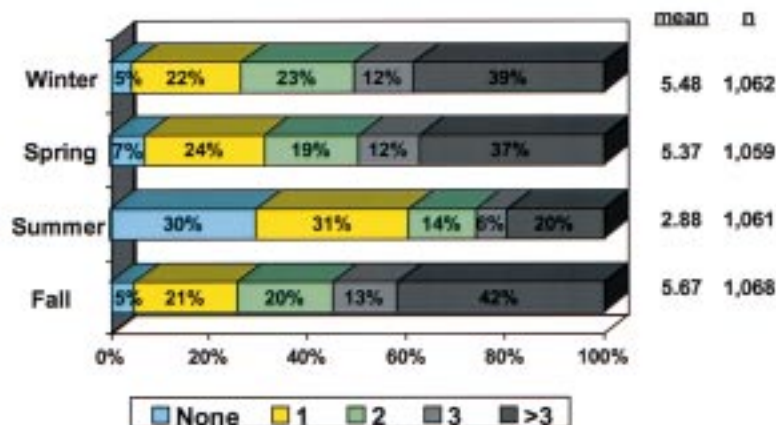


FIG 7. Seasonal pattern of asthma exacerbations (number of exacerbations per month) during each of the seasons in children. The percentages represent the proportion of respondents who experienced zero (blue), 1 (yellow), 2 (green), 3 (light grey), or more than 3 (dark grey) exacerbations per month; mean refers to mean exacerbations per month, and *n* refers to the number of respondents.

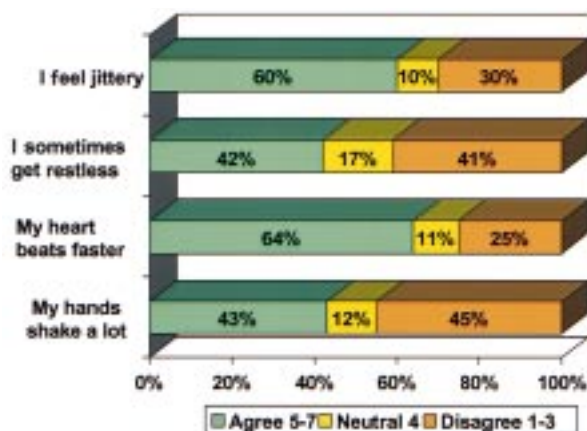


FIG 8. The answers received from adult respondents when asked about medication side effects that they ascribed to their bronchodilators. Possible responses were on a 1 to 7 scale, with 1 representing strongly disagree, and 7 representing strongly agree. The side effects listed are the 4 most common side effects reported in the adult group.

the summer, compared with 5% to 7% and 21% to 24%, respectively, in the other seasons (Fig 7). Although most parents opined that their child's asthma was well controlled, parents of both nebulizer users and oral medication users were less likely to feel that way compared with parents of MDI users (59%, 63%, and 74%, respectively; $P < .05$ for nebulizer vs nonnebulizer users). This is in contrast to the perception of the physicians who classified children in the oral group as having mild asthma. The parents' opinions were not without merit, however, because children in the nebulizer and oral medication user groups had significantly more unscheduled physician visits per year than children in the MDI group (4.8, 4.8, and 2.8 per year, respectively; $P < .05$ for nebulizer versus nonnebulizer users) and were also more likely to have been sent home from school because of asthma symptoms (39%, 42%, and 29% of the children in each

group, respectively; $P < .05$ for nebulizer vs nonnebulizer users). Interestingly, emergency room visits occurred most frequently in the oral group, followed by the nebulizer user group, then the MDI user group (1.12, 0.65, and 0.30 visits/year, respectively; $P < .05$ for oral vs MDI users and for nebulizer vs nonnebulizer users). In contrast, hospitalizations were more frequent in the nebulizer user group ($P < .05$), with no differences found between the MDI and oral user groups (0.22, 0.04, and 0.10 hospitalizations/year, respectively). These data suggest that children with asthma who are prescribed oral medications are often undertreated because of a failure of the physician to recognize the appropriate level of severity of the child's asthma. Alternatively, parents of children who have been prescribed oral medications may be less educated about the child's asthma and thus more fearful, leading to greater use of unscheduled and/or emergency physician contacts.

MEDICATIONS USED BY ADULTS

All of the adult respondents used a bronchodilator. As with the pediatric respondents, the majority of respondents (54%) reported using racemic albuterol, (compared with 77% of the nebulizer group), 43% used Serevent®, 30% used Proventil®, 37% used Ventolin®, 12.5%, 11%, 11%, 6%, 5%, and 4.5% used Proventil-HFA®, Maxair®, Atrovent®, theophylline, Theo-dur®, and Alupent®, respectively, and ≤ 2% reported using Volmax®, Brethaire®, Primatine Mist®, or other OTC bronchodilators. Anti-inflammatory medications had been prescribed for 96%, 81%, and 74% of the patients in the nebulizer, MDI, and oral groups, respectively ($p < 0.05$). The following products use was reported: prednisone (24%), Flovent® (27%), Singulair® (17%), Azmacort® (21%), Vancril® (11%), Intal® (10%), cromolyn (3%), Aerobid® (8%), Tilade® (7%), methylprednisolone (3%), Pulmicort® (6%), and Beclovent® (5%). The majority of adult respondents used MDI (72%, mean age 53.5 years)

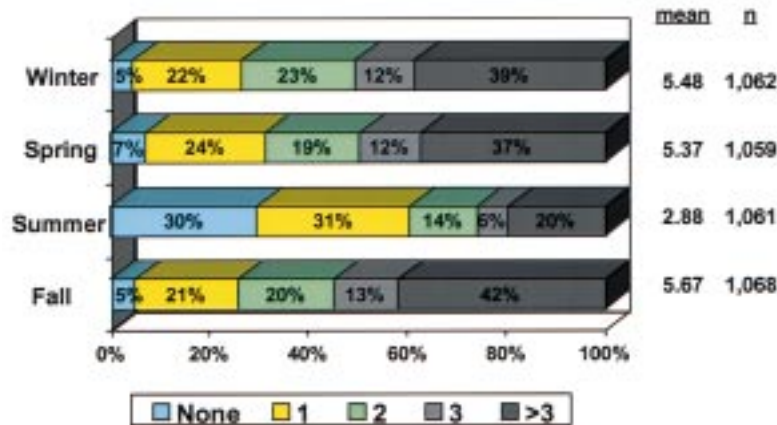


FIG 9. Seasonal pattern of asthma exacerbations (number of exacerbations per month) during each of the seasons in adults. The percentages represent the proportion of respondents who experienced zero (blue), 1 (yellow), 2 (green), 3 (light grey), or more than 3 (dark grey) exacerbations per month; mean refers to mean exacerbations per month, and *n* refers to the number of respondents.

compared with 27% and 6% using nebulizers (mean age 51.7 years) and oral medications (mean age 55.9 years), respectively. The nebulizer users were no more likely to receive Intal or cromolyn sodium, suggesting that the nebulizers were primarily used to deliver bronchodilators.

MEDICATION SIDE EFFECTS IN ADULTS

Most respondents had experienced unwanted side effects from their medications (79%, 63%, and 74% of the nebulizer, MDI, and oral medication groups, respectively), with a greater proportion of nebulizer users reporting multiple untoward effects (Fig 1; $P < .05$ for nebulizer vs nonnebulizer users). Only a small proportion of respondents felt their medication side effects to be coming strictly from their anti-inflammatory medications alone (15%, 14%, and 8% of the nebulizer, MDI, and oral groups, respectively). The most common bronchodilator side effects reported by adults were tachycardia (64%), jitteriness (60%), shaky hands (43%), and restlessness (42%; Fig 8). All 4 of these untoward effects were observed most commonly in the nebulizer users (70%, 65%, 52%, and 55%, respectively; $P < .05$ for all side effects except jitteriness) than in the nonnebulizer users. Effects observed less frequently than in 40% of all respondents that were observed more often in the nebulizer users included cough, difficulty falling asleep, trouble writing neatly, skipped heart beats, sore throat, difficulty concentrating and feeling spacey, and having too much energy (51%, 46%, 42%, 36%, 35%, 35%, and 21%, for the nebulizer users, respectively; $P < .05$ for all side effects).

Although most respondents (73%) had spoken to their physicians about their side effects, the nebulizer and oral medication users were more likely to have complained (Fig 3; $P < .05$ for nebulizer vs nonnebulizer). The most common physician response (28%-35%) was to change the drug (often to another form or brand). Dosing adjust-

ments were made approximately 16% to 26% of the time (Fig 4). As with the pediatric patients, adult patients were frequently told that side effects were to be expected and that the benefits outweighed the side effects. Fewer than 4% of respondents in either group regarded their physicians as "caring/sympathetic/willing to listen/discuss their bronchodilator side effects." Thirty-three percent of adult respondents had reduced the dose or frequency of their bronchodilator to attenuate side effects (Fig 5); 24% had actually skipped doses without instructions from their physician to avoid side effects (Fig 6). Thus these data suggest similarity in the type and frequency of bronchodilator side effects experienced by pediatric and adult patients with asthma. However, physicians are more likely to make adjustments to their adult patient's medications, possibly because of an expanded array of therapeutic choices for treating adults as compared with children.

MARKERS OF ASTHMA CONTROL IN ADULTS

Adults also experienced fewer asthma exacerbations in the summer months (Fig 9), although the contrast with the rest of the seasons was not as marked in the adults as compared with the children (18% of adults reported no exacerbations in the summer, compared with 6%-8% during the other seasons). Most adult nonnebulizer users felt their asthma to be under good control (64% of the MDI users and 73% of the oral medication users), compared with only 41% of the nebulizer users ($P < .05$). This is in agreement with the assessments of their physicians who classified significantly more nebulizer users as severe (55%, 20% and 32% of the nebulizer, MDI, and oral groups, respectively; $P < .05$). A larger proportion of the nonnebulizer user group was classified as having moderate asthma (39%, 47%, and 61%, for nebulizer, MDI, and oral groups, respectively), although respondents classified as mild were more likely to be prescribed

MDIs (10%, 35%, and 18% of nebulizer, MDI, and oral groups, respectively). Indeed, the nebulizer user group experienced significantly more unscheduled office visits (4.3, 1.8, and 1.9 per year for nebulizer, MDI, and oral groups, respectively; $P < .05$), more emergency room visits (0.82, 0.29, and 0.13 per year for nebulizer, MDI, and oral groups, respectively; $P < .05$), more hospitalizations (0.67, 0.06, and none per year for nebulizer, MDI, and oral groups, respectively; $P < .05$), and more missed work days (5.0, 2.6, and 1.2 days per year for nebulizer, MDI, and oral groups, respectively; $P < .05$). Thus in contrast to the pediatric asthma respondents, increased use of medical resources was seen primarily in the nebulizer user group, which was more likely to contain patients who had been classified by their physicians as having severe asthma.

CONCLUSIONS

A number of asthma studies have incorporated quality-of-life questionnaires designed to measure the ability of the asthmatic patient to function normally. However, published data on the quality and frequency of bronchodilator side effects in the general asthmatic population are lacking. The results of this questionnaire suggest that unpleasant side effects of bronchodilators are experienced frequently by both pediatric and adult asthma patients. Nebulizer users of all ages, as well as pediatric patients with asthma who are taking oral bronchodilators were most likely to experience unwanted medication-related symptoms. Patients or their parents will frequently not volunteer information about side effects unless prompted to do so by the physician. These data underscore the need for physicians to be diligent in questioning patients about medication side effects. Having elicited the information, however, the physician is left with a limited range of options if the patient is experiencing side effects from their racemic β -agonists because of the necessity to use in all patients an "as needed" bronchodilator with rapid onset of action. β_2 agonists are the most effective drugs for this purpose, but their therapeutic effects and their untoward effects are mediated through the same β_2 receptor. Thus the development of

novel, rapidly acting bronchodilators with fewer side effects could enhance the quality of life of most individuals with asthma.

Hospitalizations were low in both adults and children and, not unexpectedly, occurred most frequently in patients requiring nebulized medications. However, other measures of disease control (such as unscheduled office visits, emergency room visits, and being sent home from school/work because of asthma symptoms) occurred with increased frequency in the pediatric but not the adult oral medication group. This was unexpected, because the physicians had rated these patients taking oral medication as having mild asthma. These data suggest that, although hospitalization frequency may be a good index of physiologic asthma control, other control measures (such as emergency visits, unscheduled office visits, and time missed from school/work) may be better indicators of psychologic asthma control. Discordance between these 2 indices may suggest the need for more intense asthma education and/or specialty referral.

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