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REVIEW

Achieving asthma control in practice: Understanding the reasons for poor control

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Summary
Achieving asthma control remains an elusive goal for the majority of patients worldwide. Ensuring a correct diagnosis of asthma is the first step in assessing poor symptom control; this requires returning to the basics of history taking and physical examination, in conjunction with lung function measurement when appropriate. A number of factors may contribute to sub-optimal asthma control. Concomitant rhinitis, a common co-pathology and contributor to poor control, can often be identified by asking a simple question. Smoking too has been identified as a cause of poor asthma control. Practical barriers such as poor inhaler technique must be addressed. An appreciation of patients' views and concerns about maintenance asthma therapy can help guide discussion to address perceptual barriers to taking maintenance therapy (doubts about personal necessity and concerns about potential adverse effects). Further study into, and a greater consideration of, factors and patient characteristics that could predict

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individual responses to asthma therapies are needed. Finally, more clinical trials that enrol patient populations reflecting the real world diversity of patients seen in clinical practice, including wide age ranges, presence of comorbidities, current smoking, and differing ethnic origins, will contribute to better individual patient management.

Contents

Introduction

Achieving asthma control remains an elusive goal for the majority of patients worldwide.[1–3] This troublesome reality persists despite the availability for over two decades of international asthma management guidelines and asthma therapies of proven efficacy, at least for the highly selected patient populations studied in controlled trial settings.[4,5] Poor asthma control places a heavy burden on patients and their families, as it manifests in increased rates of hospitalisations and emergency room and other urgent care visits, in addition to activity limitations, night-time awakenings, and lost time from work and school.[6] Moreover, poor asthma control is expensive, accounting for most of asthma-related health-care costs.[7]

An international initiative was begun in 2006, under the auspices of the International Primary Care Respiratory Group (IPCRG), to examine the reasons for poor asthma control and arrive at a consensus on how best to improve the delivery of asthma care in the primary care setting, where most patients with asthma are managed. The first discussion centred around understanding the patient's perspective as a means of improving asthma control.[8] A key priority emerging from this discussion was the need to identify and develop validated instruments (tools) to assess asthma control and understand the reasons for poor control for individual patients. Primary care providers work under tight time constraints and often with limited diagnostic facilities. Therefore, tools for use in primary care must be simple and practical.

Building on the first discussion, a second meeting was held in September 2007 to examine common reasons for poor asthma control and how these might be identified and addressed in clinical practice. Here we report the discussion of these important issues, including what sort of tools could

be used to identify and correct specific causes of poor control, namely, the wrong diagnosis, poor inhaler technique, smoking, co-morbid rhinitis, individual variation in response to treatment, and poor adherence to treatment.

Reasons for poor asthma control: the wrong diagnosis

Patients may be given a diagnosis of asthma on the basis of a compatible history and a successful trial of therapy. If asthma symptoms do not respond as expected to treatment, an important step—before increasing doses or adding medications—should be to review and attempt to confirm the diagnosis of asthma. Other conditions share common features with asthma, and other confounding illness, such as allergic rhinitis, can worsen asthma symptoms.

Asthma diagnosis: the basics

Returning to the basics of making a diagnosis is essential. This includes a thorough history, physical examination, and appropriate diagnostic testing. Ideally, a diagnosis of asthma should be based on objective evidence of reversible airflow obstruction. Because asthma is a variable disease, challenge testing may be required. Normal spirometry results do not exclude the diagnosis. Spirometry, it seems, is not always performed, even when the equipment is available.[1] Moreover, many primary care clinicians worldwide may not have the equipment or sufficient time or experience to measure peak expiratory flow (PEF) or to perform accurate and reliable spirometry.

Measures of inflammation, when they become available, may also become useful. Other options for diagnosing asthma are validated asthma questionnaires such as those contained in the IPCRG guidelines,[9] which help diagnostic decision-making.

Diagnosing asthma in adults

Some of the symptoms of asthma are shared with diseases of other systems. Thus, the differential diagnoses for adults include respiratory and non-respiratory causes. Eliciting a thorough medical history is essential. Patients may not readily admit to smoking, occupational exposures, or exposure to other triggers such as having pets. In addition, comorbidities, such as gastro-oesophageal reflux disease, allergic rhinitis, chronic obstructive pulmonary disease (COPD), infection, cardiac disorders, and anaemia should also be treated to successfully treat asthma.

Diagnosing asthma in children

The youngest patients, those under 5 or 6 years of age, usually cannot perform the manoeuvres necessary for accurate spirometry, and the diagnosis thus rests on history, physical examination, and ancillary testing. In this age group, differential diagnoses also include respiratory (upper and lower) as well as non-respiratory causes.

Young children commonly wheeze with colds. A clinical index of asthma risk aids in identifying children with recurrent wheeze $\geq$2 years of age who are more likely to develop persistent asthma: For children who have had four or more wheezing episodes, the likelihood of asthma is greater if they have one of three major risk factors (parental history of asthma, personal history of physician-diagnosed eczema, or allergic sensitization to $\geq$1 aeroallergen) or two of three minor risk factors (allergic sensitization to milk, egg, or peanuts, wheezing apart from colds, and eosinophilia of $\geq$4%).[10]

It is useful to attempt to decide which phenotype of childhood asthma is present to predict therapy needs and duration.[11,12] Transient childhood wheezers with no other allergic diathesis often wheeze with respiratory viral infections because of their smaller airway calibre and the fact that resistance to airflow increases with smaller calibre.

Reasons for poor asthma control: incorrect choice of inhaler, poor technique

Poor inhaler technique is a common problem among patients with asthma, and asthma control worsens as the number of mistakes in technique increases (Fig. 1).[13] Asthma guidelines stress the importance of patient training in inhaler use.[5,14] Moreover, trainers should be competent, and inhaler technique should be rechecked at every routine asthma consultation with patients demonstrating their inhalation technique.

When inhaler devices are used correctly, there is no clinical difference between devices.[15,16] However, each inhaler type requires a different pattern of inhalation for optimal drug delivery to the lungs. Each patient must be able to use their device correctly to obtain optimal benefit. If possible, device types should not be mixed for any individual patient.

The choice of inhaler for corticosteroid delivery is most important because of the greater need to specifically and accurately target the site of deposition. The choice of inhaler for reliever bronchodilator therapy is less important because of a wider therapeutic window; the patient can compensate for poor technique by taking another inhalation if the desired effect is not achieved.

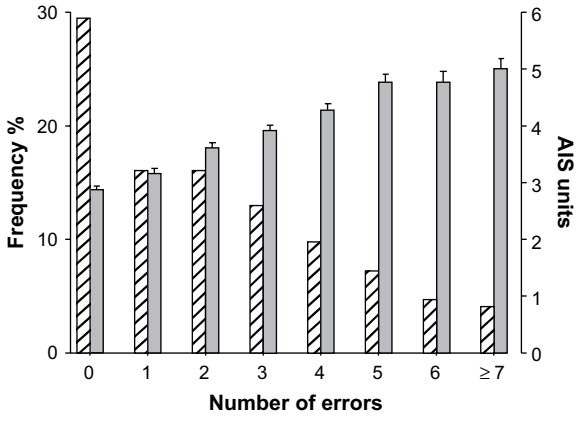

Figure 1 Misuse of pressurised metered dose inhalers is directly linked to decreased asthma stability: frequency distribution of the number of errors or omissions in inhalation technique (left axis; striped bars) and relationship between this number and the Asthma Instability Score (AIS; mean $\pm$ SEM, right axis; grey bars). Correlation between the number of errors and AIS (linear regression analysis): $r = 0.3$, $p < 0.0001$. Reprinted with permission from Giraud et al.[13]

Device choice

Currently available inhalers include (1) pressurised metered-dose inhalers (MDIs), (2) breath-actuated MDIs (BAIs), and (3) dry powder inhalers (DPIs).

Lung deposition of drug varies according to fine particle dose (particles $<5\ \mu m$) and characteristics of the particle size range, as well as by inhaler device, ranging from as low as 7% with beclometasone delivered by chlorofluorocarbon (CFC)-propellant MDI to as high as 55% with extra-fine beclometasone delivered by CFC-free hydroflouroalkane (HFA)-propellant MDI. Lung deposition of beclometasone or budesonide by DPI is intermediate ($\sim$33%).[17] The use of a spacer (with an MDI) approximately doubles lung deposition.

Oropharyngeal deposition of an inhaled corticosteroid (ICS) is important with respect to local side effects. Factors that determine deposition in the mouth and throat are particle size and the speed of inhalation, as well as the velocity of the spray from an MDI. Inhaling from a spacer device greatly reduces oropharyngeal deposition when using a CFC-propellant MDI, whereas a spacer device may not be as important for the new extra-fine CFC-free beclometasone formulations, as the particles are smaller and the force of the spray is less. A DPI has to be inhaled with a fast inhalation hence there is a lot of oropharyngeal impaction in the mouth and throat.

Metered-dose inhalers

MDIs are often used incorrectly[13]; therefore, it is important that patients be trained to use them correctly. MDIs require a slow and deep inhalation over 5 s with coordination between dose release and the start of the inhalation. However, only 8% of patients inhale slowly and deeply with good coordination during routine use with their MDI.[18] MDIs can be used with spacers, large or small; however, a spacer is the inhalation method least preferred by patients.[19]

The most common mistake patients make with these devices is to inhale too fast.[20,21] Other common problems include poor coordination of actuation and inhalation (solved by training or switching to a BAI); stopping after inhalation when the cold spray hits the back of the throat (''cold Freon effect'', solved by adding a spacer or switching to CFC-free propellant); and inhaling through the nose (solved through training).

If the patient uses a slow and deep inhalation, then good coordination is not critical as long as the patient is inhaling when they release the dose from an MDI.[22] However, despite training, patients will revert back to their bad habits.[23] It has been shown that lung deposition is less affected by inhalation flow if the particles that are emitted from an inhaler are ultrafine.[24] Some of the reformulated CFC-free propellant corticosteroid MDIs deliver ultrafine particles and thus help overcome the problem of inhalation speed. Moreover, use of a BAI, easier to use than a traditional MDI, can translate to improved outcome in terms of better asthma control.[25]

Dry powder inhalers

DPIs require a rapid acceleration rate during the initial part of the inhalation manoeuvre to transform the metered dose into a quality dose that has the greatest potential for lung deposition. In the past the emphasis has been on the peak inhalation rate, but if this is reached slowly by the patient, then the initial acceleration rate may be insufficient to produce the required quality dose. Failure to inhale deeply and forcibly at the start of the inhalation manoeuvre means that the drug particles generated are too big to enter the lungs and are simply deposited in the mouth and oropharynx where they have no clinical efficacy. Moreover, if the patient does not inhale fast enough or long enough, not all the dose is emitted.[26]

Young children have trouble achieving the minimum rate of inspiratory flow and thus DPIs should not be prescribed to children <5 years old.[27] Sensitive to moisture, DPIs should be stored in a dry place, and patients should take care not to blow into the inhaler, as this will affect dose delivery.

Devices to aid inhaler technique

Schematic cartoons illustrating inhaler technique for several devices are available on the Asthma UK website[28]; and inhaler and spacer diagrams are available on the GINA website.[29] In addition, relatively inexpensive devices to check technique and maintain trained technique are now available, and more are being developed, such as the Aerosol Inhalation Monitor (AIM, Vitalograph Ltd, Buckingham, England); the 2Tone Trainer (Canday Medical Ltd., Newmarket, England); the AeroChamber Plus spacer (Forest Pharmaceuticals, Inc., St. Louis, US); and the In-Check Dial (Clement Clarke International Ltd., Essex, UK). The Turbuhaler whistle (AstraZeneca International, London, UK) is an example of a simple device that has been introduced to check for the required inhalation rate for patients prescribed this device. The Novolizer (MEDA Pharma GmbH & Co. KG, Bad Homburg, Germany) has been designed to release its dose only when the required inhalation rate is achieved.

Beyond device choice—improving inhaler technique

When choosing an inhaler device, it is important to take account of patients' preferences and views, as well as to simplify the regimen and not mix inhaler types. Patients should be trained to use their inhaler devices properly, and their technique should be rechecked on each revisit. Observation of technique by a health professional or by patients themselves, perhaps on video in some settings, can be useful to detect problems. Use of more tolerant devices, such as BAIs, can be helpful for some patients. Finally, oral controller therapy (antileukotriene) is a consideration for patients with mild to moderate asthma who continue to have difficulty with their inhaler. Licensing approval for this option varies in different countries and for different age groups.

Reasons for poor asthma control: smoking

There is clear evidence now that concurrent smoking adversely impacts asthma control. The prevalence of current smoking among patients with asthma varies by country from 15% to 25%.[30,31] In a retrospective cohort study of a large UK

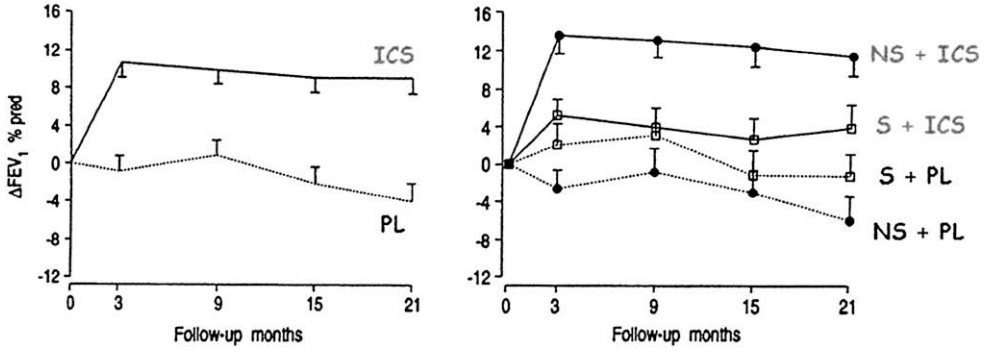

Figure 2 Effect of inhaled corticosteroid (ICS) therapy versus placebo (PL) on lung function among patients with chronic asthma. Baseline FEV_1 improved significantly in the ICS-treated arm compared with placebo. However, when dividing the patients according to smoking habit (S = current smoker, NS = nonsmoker), the effect on lung function was seen only among the non-smoking patients. Adapted with permission from Kerstjens et al.[33]

general practice database, current smokers were almost 3 times more likely than non-smokers to be hospitalised for their asthma over a 12-month period.[32]

Suboptimally controlled asthma in smokers may be the result of concomitant COPD or asthma misdiagnosed as COPD. An alternative explanation is that ICS therapy fails more often in smokers. Studies of smokers with asthma indicate that these patients respond differently to corticosteroids than do non-smokers.

In one Dutch study, the effect of ICS was compared with placebo, using lung function and airway hyperresponsiveness as primary outcome variables.[33] A highly significant improvement in FEV_1 was found in the arm treated with ICS compared with placebo. However, when the patients were segmented according to smoking status, benefits were noted only in the non-smoking group (Fig. 2). A study published in 2002 further illustrates the lack of effects of ICS for treating patients with asthma who smoke: in this study of patients with mild asthma, fluticasone had no effect on lung function or sputum eosinophils in smokers (Fig. 3).[34]

Eosinophil and neutrophil activity in smokers is not reduced by ICS therapy, even at high doses.[35] Moreover, the correlation between exhaled nitric oxide, a marker of eosinophilic airway inflammation, and airway hyperresponsiveness is lost in smokers.[36] Administration of high-dose ICS therapy did not improve lung function among smokers with asthma in one study,[35] and results were not definitive in a second study.[37]

Reasons for relative corticosteroid resistance among smokers with asthma

There are three reasons currently proposed for the relative corticosteroid resistance among smokers with asthma. Firstly, the pattern of airway inflammation in smokers is different from that in non-smokers with asthma: smokers have a higher percentage of neutrophils in induced sputum,[38] and corticosteroids are not very effective in reducing neutrophils. Among patients who stop smoking, there is a large reduction in sputum neutrophil count.[39] Thus, neutrophilic inflammation responds to smoking cessation but not to corticosteroids.

Secondly, smoking produces oxidative stress, which impairs the activity of histone deacetylase-2 (HDAC2),[40] resulting in reduced anti-inflammatory activity of corticosteroids. Finally, smoking triggers leukotriene production in patients with asthma, and leukotrienes are not reduced by corticosteroid therapy.[41]

Clinical approach to patients with asthma suspected or known to smoke

These findings highlight the importance of identifying current smoking habits of patients with asthma, particularly those whose symptoms are poorly controlled. While an oral history may not elicit this fact, patients may admit to smoking when asked via a written self-completed questionnaire, as they may feel less threatened. For patients who are suspected or confirmed smokers, the consultation should include investigations to exclude COPD.

The ideal therapy for patients with asthma who smoke is smoking cessation.[42] In the absence of that, therapeutic

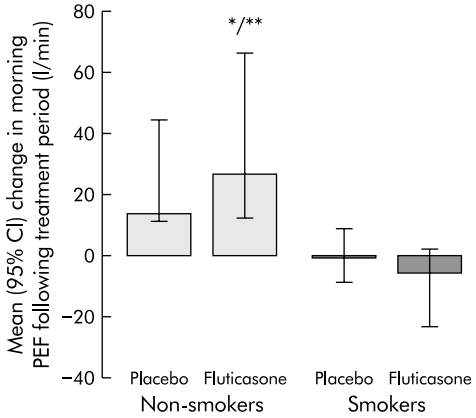

Figure 3 Mean (95% CI) peak expiratory flow (L/min) in non-smoking and smoking patients with asthma after treatment with inhaled placebo or fluticasone propionate 1000 μg/day. $*p = 0.016$, greater than non-smokers after placebo; $**p = 0.001$, greater than smokers after fluticasone. From Chalmers et al.[34] Reproduced with permission from the BMJ Publishing Group.

alternatives to low-dose ICS are a leukotriene receptor antagonist (LTRA), theophylline, or possibly high-dose ICS (up to 1600 μg/day).

The LTRA montelukast seems to have some effect in smokers with asthma, as shown by a recently performed pilot study.[43] These results need to be confirmed in larger clinical trials. From a theoretical point of view, combination therapy with ICS and long-acting β2-agonist or theophylline could have a beneficial effect in smokers. While long-acting β2-agonist was found to suppress tobacco-induced macrophage activation[44] and improve airway mucociliary clearance,[45] theophylline to some degree prevents suppression of the histone deacetylase inflammatory gene believed to be important in smoke-induced corticosteroid resistance.[46] However, convincing clinical data are lacking and thus we do not yet have any solid recommendations for how to treat this large group of patients.

Reasons for poor asthma control: co-morbid rhinitis

Asthma and rhinitis, both allergic and nonallergic, are linked in many ways: they share a similar epidemiology (most patients with asthma have rhinitis), and they have common triggers.[47–49] The pattern of inflammation is similar, involving T helper type 2 cells, mast cells, and eosinophils. Moreover, nasal challenge results in asthmatic inflammation and vice versa.[50,51] Finally, the presence of rhinitis predicts the development of asthma.[49]

Asthma patients with rhinitis use more health-care resources than those without rhinitis, indicating that their asthma is less well-controlled. In a retrospective cohort study of 27,000 adult patients with asthma included in a large UK general practice database, patients with concomitant rhinitis were 50% more likely to be hospitalised for their asthma, and significantly more likely to visit their primary care physician, over a 12-month period than those without rhinitis.[32] Moreover, the presence of concomitant rhinitis was associated with significantly higher drug use and costs among these patients with asthma. For children in a similar study, the presence of concomitant asthma and rhinitis more than doubled the likelihood of being hospitalised and significantly increased the likelihood of a physician visit for asthma.[52] All levels of rhinitis can impact on asthma control: the percentage of adult patients with poor asthma control is greater even among those with mild rhinitis, as compared with patients with asthma alone.

Clinical approach to patients with asthma and concomitant rhinitis

The question thus arises whether treatment for rhinitis will improve asthma control. While this question requires further study, preliminary data would suggest that it does. In a trial of patients with chronic moderate asthma comparing the effect of doubling budesonide versus adding montelukast, no difference was found between the two arms, using lung function and symptom control as primary parameters. However, patients with co-morbid rhinitis who received budesonide plus montelukast showed significantly greater improvement in morning PEF and other clinical outcomes than the group receiving monotherapy with doubled dose of budesonide, suggesting that the effects of a regime treating both the upper and lower airways improved lower airway function most (Fig. 4).[53] The difference became even more pronounced in the limited number of patients needing treatment for their rhinitis (see Fig. 4).

While a good history and examination of the nose will aid in the diagnosis of rhinitis, the patient's answer to a single, practical question, adapted from that used by the International Study of Asthma and Allergies in Childhood (ISAAC),[54] may be all that is needed to diagnose rhinitis:

> ''Do you have an itchy, sneezy, runny, or blocked nose when you don't have a cold?''

The inflammation of both upper and lower airways should be treated to obtain optimal clinical outcomes (Table 1).[55,56] Nasal corticosteroids may possibly improve asthma control when used in conjunction with ICS, although the evidence supporting this is limited at this point.

Reasons for poor asthma control: individual variation in response to treatment

Limitations of randomised controlled trials

Traditional, formal randomised controlled trials (RCTs) are established as the bed-rock of recommendations made by clinical guidelines. The current focus of clinical trials in asthma is driven by many factors, including regulatory requirements, history (what's been done in the past and is therefore still expected), ease of measuring certain endpoints, available technology to measure these endpoints, the needs of industry, the need to focus on short-term events of asthma (from where the most obvious costs stem, such as from hospitalisation), and the limited number of agents available for treating asthma. The design of RCTs, quite properly, usually involves attempts to remove all possible confounding factors to allow assessment of the intervention studied. This can, however, lead to difficulties with translation of the results of the study, either directly or through a guideline recommendation, due to an inability to generalise the study to a true clinical population.

The conduct of a study, often involving increased contact with health-care professionals and higher levels of education and training, may influence compliance with therapy, competence in administration, and adherence to more complex therapeutic regimes (perhaps involving multiple, perhaps dummy, therapies) than is seen in standard clinical practice. Adherence is believed to be considerably better in clinical trials than in real life and this can of course be important when a tablet is compared with an inhaled drug. In real life, adherence to ICS is usually between 30% and 40%.[57]

Regulatory authorities' decision to place a very high emphasis on lung function, particularly FEV_1, as both an entry criterion and as the primary outcome of clinical trials can both influence patient selection and also detract from other, perhaps more patient-focused, outcomes.

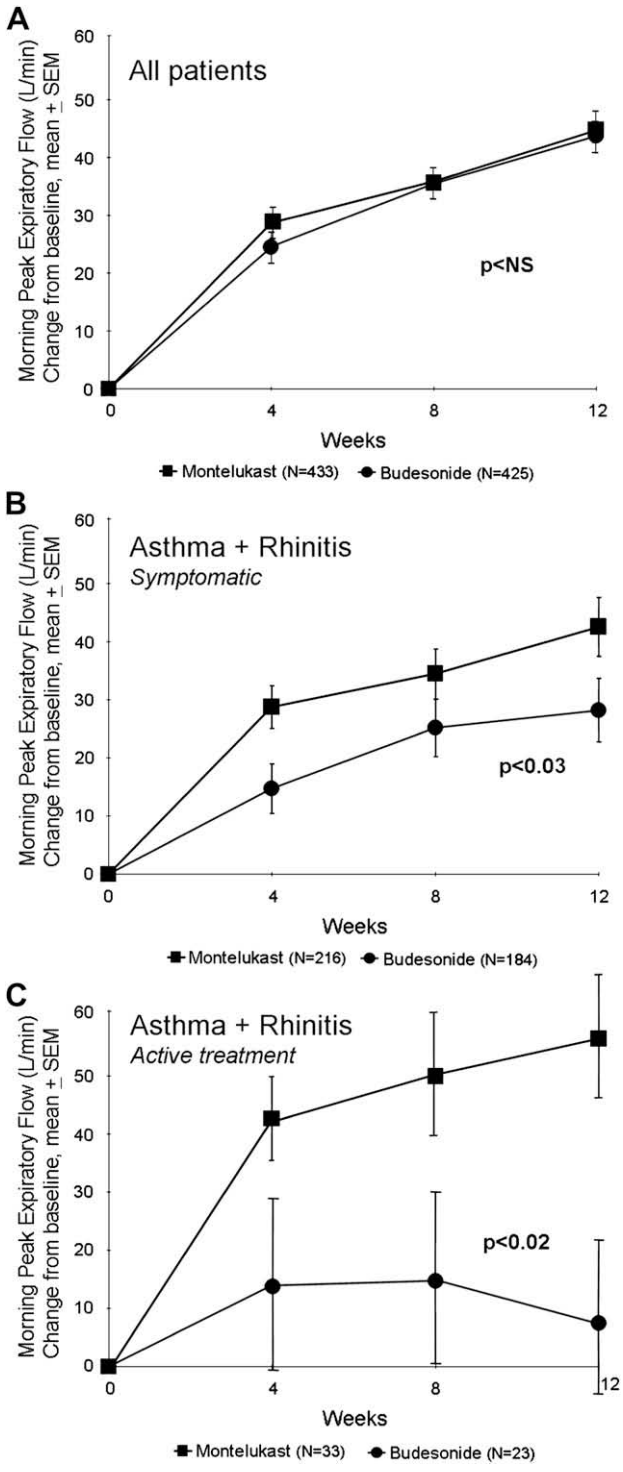

Figure 4 Change from baseline in morning peak expiratory flow for patients who received montelukast 10 mg once daily + budesonide 400 μg twice daily or budesonide 800 μg twice daily. (A) All patients, (B) patients with asthma and concomitant allergic rhinitis, (C) patients with concomitant rhinitis requiring regular treatment. From Price et al.[53] Adapted with permission from Wiley-Blackwell.

Table 1 Treatment of comorbid rhinitis and asthma

Upper airway treatment options	Lower airway treatment options
Nasal corticosteroids Antihistamines	Inhaled corticosteroids
Upper and lower airway treatment options	
1. Leukotriene receptor antagonists 2. Anti-IgE 3. Immunotherapy	

Indeed, the recommendations from the European Medicines Agency (EMEA) call for evidence of >15% reversibility in FEV_1 after short-acting bronchodilator for patients enrolled in clinical trials. This criterion alone excludes many patients with asthma from clinical trials (not all patients with asthma show substantial reversibility at one point in time), and, furthermore, selects those patients more likely to be responsive to β2-agonist. Careful selection of participants in a clinical trial can clearly influence the study's results.[58]

Clinical study patients versus real-life patients

An important question thus is whether the patient selected for a clinical trial is representative of the larger number of patients treated for asthma by physicians, namely, real-life asthma patients. The answer to this question is obviously ''no,'' as most patients with any comorbid condition are excluded from most randomised clinical asthma trials. In fact, two studies suggest that only a small percentage of people with asthma in a general practice population would satisfy all the entry criteria and none of the exclusion criteria for typical formal RCTs in asthma.[59,60]

It is a discredit to the respiratory research community that so few studies have focused on, or even included, the considerable percentage of people with asthma who smoke, and the few studies that include ''smoking asthmatics'' convincingly show that ICS treatment has marginal effects for them compared with those who do not smoke, as discussed above. Similarly, from clinical epidemiologic studies we know that the majority of patients with asthma have concomitant rhinitis and that the rhinitis component affects patients' well-being as well as interferes with treatment effect.[61]

Another important factor is patient perception of their disease, as many patients fail to perceive their level of asthma control. This factor is not unimportant when a symptom-based approach is being used to achieve optimal disease control.[62,63] The lack of perception does not seem to be related to degree of disease knowledge or any obvious personal characteristics.[64] Moreover, low perception is commonly found in patients with more severe disease,[65] with increased hyperresponsiveness and lower lung function.[66] As perception and a documented need to take extra rescue medication are common inclusion criteria in clinical trials, it is reasonable to assume that patients with low perception are being excluded.

Group mean versus individual trial data

Data from clinical trials are usually reported as group mean data. This helps us to know how best to treat a population but may not help us in the real-life clinical scenario: one patient in the clinician's office. Results of two studies comparing an ICS versus an LTRA as anti-inflammatory strategies indicate that mean data do not always apply to the individual patient.

In the study by Malmstrom et al.,[67] beclometasone was compared with montelukast for patients with chronic asthma. In the beclometasone group there was a mean improvement in morning PEF of 39 L/min, significantly better ($p < 0.001$) by an additional 64% than for montelukast (24 L/min). A completely different picture is seen, however, at an individual level analysis. An increase in FEV_1 of $\geq$11%, a clinically relevant improvement, was seen for 42% of montelukast-treated patients and 50% of the beclometasone-treated patients (Fig. 5). Moreover, the number of severe asthma exacerbations was the same for both groups.

The obvious follow-up questions to the results will be a) were the patients selected for the study representative of a larger patient population? and b) were the patients who responded positively to montelukast also by nature responders to beclometasone? Regarding patient selection, all patients had chronic persistent asthma with at least 15% confirmed reversibility to short-acting β2-agonist; about 65% had concomitant rhinitis. Unfortunately, no data were reported on response pattern in various clinical phenotypes.

Whether montelukast-responsive patients also respond to ICS was investigated in a second study comparing montelukast with fluticasone propionate for young patients with mild persistent asthma.[68] Fluticasone treatment was superior to montelukast treatment with regard to number of asthma control days, with a mean of 5 versus 4.3 asthma control days for montelukast ($p < 0.001$). However, if one examines individual response data, both treatment alternatives provided equal clinical effect in the majority of patients (60%). Moreover, in a limited number of patients ($n = 15$, or 12%), montelukast provided a better clinical effect than fluticasone (Fig. 6).

These findings clearly illustrate the need to carefully monitor treatment effect for each individual patient. A highly significant difference in the mean increases the likelihood of one drug being more effective than the other. However, to forecast the effect in a single patient requires more specific phenotypic information. For example, in the latter study,[68] a high level of exhaled nitric oxide and frequent use of rescue ß2-agonist increased the likelihood of getting a better response from fluticasone treatment. However, for most of the patients no clear relation between clinical phenotype and drug response was seen.

The presence of atopy and current smoking status are obvious examples of phenotypes easily identified in the clinical setting (although not all patients will admit to smoking!). However, even in these groups, response to treatment can vary considerably. For understandable reasons, the pharmaceutical industry has traditionally been reluctant to define subgroups of good responders, and randomised trials including a large number of carefully selected patients have been the gold standard for many years. Highly significant statistical differences between treatment modalities are easy to reach when large numbers of patients are included. However, statistical difference does not always imply clinically relevant difference. From the attending doctor's perspective it is more important to identify clinically relevant changes for the individual patient.

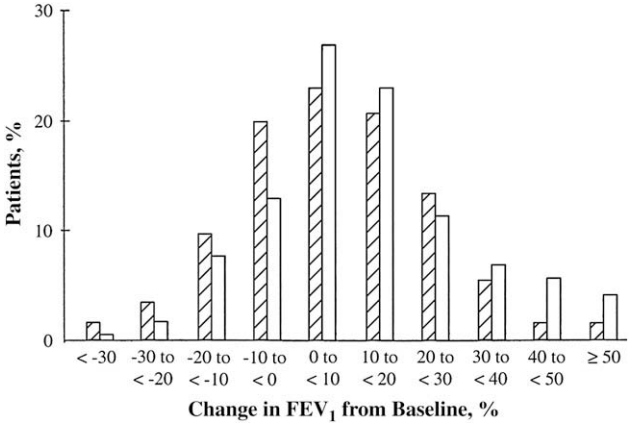

Figure 5 Distribution of clinical response measured as change from baseline FEV_1 after treatment with beclometasone 200 μg twice daily (white bars) or montelukast 10 mg once daily (striped bars). Reprinted with permission from Malmstrom et al.[67]

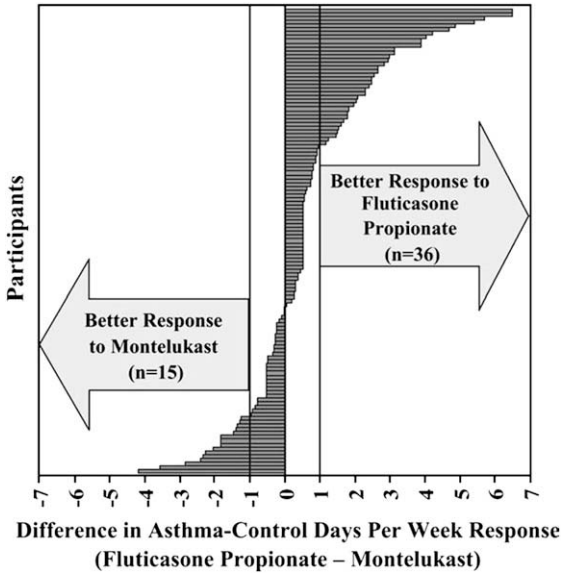

Figure 6 Response to treatment with montelukast 5—10 mg once daily compared with fluticasone propionate 100 μg twice daily in children aged 6—17 years with mild to moderate asthma. An asthma control day was briefly defined as no day- or night-time symptoms, no use of rescue medication, PEF >80% of baseline, and no social or functional limitations secondary to asthma. Each line designates a single participant. Reprinted with permission from Zeiger et al.[68]

Pharmacogenetics

Pharmacogenetic analyses may help in the future to identify potential responders. Beta-2 receptor polymorphism is one example for which studies have indicated that patients homozygous for arginine (arg/arg) at amino acid 16 on the β-receptor gene are less responsive to β2-agonist and more prone to develop tolerance to regular treatment.[69,70] This has, however, been questioned in a recent study by Bleecker et al.,[71] who could not find obvious differences between the genotypes. Other studies have found genetic variability in the 5-lipoxygenase gene identifying subtypes less prone to respond to 5-LO inhibitors[72] and genetic polymorphism on the LTC_4-synthase gene possibly identifying different responders to LTRA treatment.[73] However, the results produced so far are not definitive, and the field of pharmacogenetics needs to be further developed before findings can be used with confidence in clinical practice.

Reasons for poor asthma control: patients' beliefs and adherence

Prescribed treatments are effective only if taken. Patient nonadherence to treatment is an important problem across chronic illnesses, with as much as 30—50% of prescribed medications not taken as directed.[74,75] This level of nonadherence represents a loss to health-care systems, because of wasted resources and costs of inadequate treatment, and to patients, because of the missed opportunity for improving health.[76]

In asthma, nonadherence to controller therapy, especially ICS, is common and is likely a factor in poor asthma control.[77,78] However, nonadherence is often a hidden problem because it is not commonly assessed at routine asthma visits. Patients may be reluctant to admit nonadherence to avoid disappointing their physician, and physicians may be reluctant to query about adherence because they lack a clear and easy method to improve it. Formal interventions to improve adherence have not been successful,[79] perhaps because of lack of complete understanding about the causes of nonadherence.

The perceptual-practical model of nonadherence

Causes of nonadherence can be broken down into two categories: unintentional and intentional nonadherence.[76,80] *Unintentional nonadherence* results from practical barriers to treatment, such as language barriers, forgetfulness, and inadequate understanding of the instructions. Poor inhaler technique falls under this category. *Intentional nonadherence* results from patient choice to take less medication than prescribed (or none), or to take it differently than prescribed.

The term *concordance* describes the degree to which the patient and health-care provider agree about the nature of the patient's illness and chosen treatment path.[76,81] As such, concordance (1) recognises that patients and health-care providers bring to the consultation two sets of (potentially opposing) beliefs about the illness and treatment, and (2) incorporates a presumption of adequate communication between patient and health-care provider. When beliefs differ, and the patient and provider fail to reach an understanding during the consultation, no concordance is the result, and patient nonadherence to treatment is more likely.

Assessing necessity beliefs and concerns: the necessity-concerns framework

Intentional nonadherence is often related to patients' personal beliefs about treatment, particularly the way in which they judge their personal *need* for treatment relative to their *concerns* about potential adverse effects, with low adherence associated with doubts about necessity and with concerns. This framework seems to explain nonadherence across many chronic illnesses. Both factors are relevant in most situations, and there may be an interplay between them: for example, in a situation of low necessity, concerns may become more salient. Types of concerns and, more commonly, levels of concerns vary from individual to individual, and there may also be cultural differences.[82]

In asthma, patients often doubt the *necessity* of taking a daily medication for a condition that they experience episodically. For example, in the worldwide AIRE survey, people commonly underestimated the seriousness of their symptoms (and overestimated control of their asthma).[1] Moreover, patients often have *concerns* about potential side effects from taking ICS. In a recent study, patients' beliefs about ICS were shown to correlate with their adherence, as measured both by self-report as well as by pharmacy prescribing records.[83]

Tools to assess patients' beliefs and identify adherence behaviour

Interventions to facilitate optimal adherence are likely to be more effective if they identify adherence behaviour, identify the mix of perceptual and practical barriers for the individual, and tailor the intervention and support according to specific barriers and patient preferences. Nonadherence is relevant, of course, only if asthma symptoms are poorly controlled.

The Beliefs about Medicines Questionnaire (BMQ) was developed to measure necessity beliefs and concerns and has been validated for use in a range of chronic illnesses, including asthma.[84] An-11 item asthma-specific version can be used to identify patients' doubts about the necessity of taking controller medication and concerns about potential adverse effects. Patients are asked if they agree or disagree, on a 5-point scale, with the statements.

The Medication Adherence Report Scale (MARS) was developed to assess patient adherence, with the goal of facilitating honest self-report.[85] The MARS for measuring adherence to ICS therapy consists of five statements described as being ''ways in which people have said that they use their preventer inhaler.'' The patient is asked whether their way of using their own preventer inhaler applies to the statements.

The Minimal Asthma Assessment Tool (MAAT) is being pilot-tested in the UK as a paper or online questionnaire. This simple, self-administered patient questionnaire incorporates the short clinical version of the BMQ and MARS in addition to questions assessing asthma control, the presence of smoking or rhinitis, any practical difficulties

with treatment, as well as the extent of a patient's doubts about the necessity of taking controller medication for asthma and concerns about associated side effects.[86]

Reasons for poor asthma control—summary and next steps

Reviewing the diagnosis of asthma is the first step in assessing poor symptom control. Differential diagnoses vary by age, and tools developed to aid asthma diagnosis need to reflect this. A simple question can identify patients with concomitant rhinitis, a common reason for sub-optimal asthma control. Smoking is another factor that is now a well-established cause of poor asthma control. Patients may be more likely to admit to current smoking on a written questionnaire than during a face-to-face consultation.

Preliminary results from the MAAT[87] suggest that this simple, easy-to-complete tool might assist asthma review in primary care. Eliciting patients' views about therapy could help guide discussion to address perceptual barriers to taking maintenance therapy (doubts about personal necessity and concerns about potential adverse effects) and practical barriers such as poor inhaler technique. Tools such as the MAAT that are completed by the patient before the consultation, that reflect the patient's perspective back to the clinician, can save valuable clinic time, because the findings can serve as a starting point for discussion and problem solving during the consultation, rather than the consultation period being spent in identifying problems.

Strategies to develop open, communicative, non-judgemental relationships with patients and to let patients take an active part in the planning process have been stressed.[88] In this way the caregiver can adopt a partnership approach to asthma management. There is increasing evidence that patient-focused strategies, including shared decision-making and individualised verbal and written information, can improve the patient's experience.[89]

One area that remains challenging is poor inhaler technique. The development of videos demonstrating proper technique and care for each inhaler type could be useful in this regard albeit there are practical hurdles to overcome.

All tools for aiding asthma diagnosis and management in primary care will require translation into local languages as well as adaptation to address cultural differences in perceptions about asthma, in particular the stigma associated with an asthma diagnosis that is present to varying degrees in many countries. Moreover, tools will require rigorous testing to address issues of low levels of health literacy in many countries.[89]

To support these efforts, further study is needed regarding the factors and patient characteristics that could predict individual responses to asthma therapies, and it is important that future research address this vital issue. Identifying these factors will require studies to map response distributions to different therapies according to patient characteristics and comorbidities. In addition, information is needed from clinical trials that enrol patient populations reflecting the real world diversity of patients seen in primary care, including wide age ranges, presence of comorbidities, current smoking, differing ethnic origins, and cultural diversity. Specific asthma phenotypes may be difficult to study but nonetheless require study to identify optimal treatment. Ultimately, we hope this information can be incorporated into tools to help clinicians to optimise asthma therapy and to greater enable each patient to have full quality of life with minimal or no impediment from their asthma.

Conflict of interest

John Haughney: J.H. has acted as a consultant or received support or reimbursement from AstraZeneca, GlaxoSmithKline, Merck, Sharpe and Dohme, Novartis, and Teva.

David Price: D.P. has consultant arrangements with Aerocrine, Boehringer Ingelheim, Dey Pharmaceuticals, GlaxoSmithKline, Merck generics, Merck, Sharpe and Dohme, Novartis, Schering-Plough, and Teva. He or his team have received grants and research support for research in respiratory disease from the following organisations: UK National Health Service, Aerocrine, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Sharpe and Dohme, Novartis, Pfizer, Schering-Plough and Teva. He has spoken for Boehringer Ingelheim, GlaxoSmithKline, Merck, Sharpe and Dohme, and Pfizer.

Alan Kaplan: A.K. has lectured for and has sat on or sits on Advisory Boards for Altana/Nycomed, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck/Frosst, Novartis, Pfizer, and Teva pharmaceutical companies. He also sits on a Health Canada committee.

Henry Chrystyn: H.C. has been a consultant to and received grants to attend conferences from the pharmaceutical industry. Also he has received research grants and equipment from the pharmaceutical industry for his research group. The pharmaceutical companies are Aerogen, Altana Pharma, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Innovata Biomed, Meda Pharmaceuticals, Merck Sharp & Dohme, Omron, Orion, Ranbaxy, TEVA UK, and Trinity-Chiesi. He has no personal shares with any pharmaceutical company.

Rob Horne: R.H. has had occasional paid consultant arrangements with a range of pharmaceutical companies and health-care providers. He is a director of Optimum Patient Care Ltd, which provides audit and respiratory research services to GPs. He has received grants and research support from the following organisations: Charitable Foundation of Guy's and St Thomas' Hospitals, Asthma UK, Department of Health (Policy Research Programme Research), Gilead Life Sciences, Hayward Medical Communications/Shire Pharmaceuticals. He has no personal shares with any pharmaceutical company.

Nick May: N.M. has consultancy arrangements with AstraZeneca and Merck/MSD.

Mandy Moffat: M.M. has no conflict of interest to declare. She has no shares in any pharmaceutical company.

Jennifer Versnel: J.V. has received money from Novartis, Astra Zeneca, and Nycomed to travel to ATS and ERS conferences over the past 3 years. She holds no shares in any pharmaceutical company.

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Alf Tunsäter: A.T. has produced written documents and/or lectured for and/or sits on Advisory boards for AstraZeneca, GlaxoSmithKline, Pfizer, Boehringer Ingelheim, Orion Pharma, Schering-Plough, Novartis, MSD, Pharmacia & Upjohn, Draco Läkemedel, and AGA/Linde Gas Therapeutics. He has also received research support from AstraZeneca, GlaxoSmithKline, and Schering-Plough. He has no personal shares in any of the companies.

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Supplementary data

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