The size of the problem of managing asthma

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Summary 
Asthma is now the commonest chronic disease in industrialised countries and its prevalence is rising throughout the world. However, despite the availability of very effective treatments many patients with asthma have poorly controlled symptoms and frequent exacerbations, some of which require hospital admission. Important factors contributing to poor asthma control are failure to recognise asthma as a diagnosis, non-implementation of asthma management guidelines and patient non-compliance with therapy. The guidelines themselves have many inherent limitations. Chief among these is that the evidence upon which they are based may be misleading. The evidence used to support recommendations in guidelines is derived from double-blind, placebo-controlled studies in very carefully selected patients who are usually compliant with therapy and instructed in the use of inhalers. In the 'real world' things are very different and patients frequently fail to understand how to use their therapy and are often non-compliant. Reasons for non-compliance are complex and include complicated drug and dosing regimens and inability to use inhaler devices correctly; particularly pressurised meter dose inhalers (pMDIs) due to difficulty co-ordinating device activation and inhalation. Dry powder inhalers (DPIs) preclude the need to co-ordinate inspiration with activation, are easy and convenient to use and are environmentally friendly. There is no doubt that the type of inhaler is just as important as the class of drug in the long-term management of asthma. Improvements in inhaled drug delivery will continue to be important in improving asthma management.

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Abbreviations: AIRE, Asthma insights and reality in Europe; DPI, Dry powder inhaler; GINA, Global Initiative for asthma control; ICS, Inhaled corticosteroid; LABA, Long-acting β2-agonist; PEF, Peak expiratory flow; pMDI, Pressurised meter dose inhaler; SABA, Short-acting β2-agonist

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Introduction

The size of the asthma problem remains an enormous one. The incidence of asthma continues to rise throughout the world and has been estimated to have approximately doubled over the last 10 years, with the highest incidence occurring in children, and particularly in the youngest age groups. Furthermore, studies from...
the previous two decades have suggested an increase in asthma prevalence worldwide of 5–6%, with asthma affecting 8–10% of children and 3–5% of the adult population. Worryingly, there is still a tendency to under-diagnose asthma, and consequently underestimate the true prevalence of the disease. Although asthma is still a relatively infrequent cause of death, the rates of death from asthma have risen in many countries in Europe, as well as in Canada and the United States, but have tended to decrease since 1998, perhaps due to better management.

We now know more about asthma than ever before. It is a highly complex inflammatory disease of the airways in which many cells and cellular elements play a role, such as eosinophils, mast cells, T-lymphocytes, macrophages, dendritic cells, neutrophils and epithelial cells. These cells can influence airway function through secretion of mediators that act either directly on the airway or indirectly through neural mechanisms. Cell-derived mediators can influence airway smooth muscle tone, modulate vascular permeability, activate neurons, stimulate mucus secretion and produce characteristic structural changes in the airway. Structural changes include basement membrane thickening, hypertrophy and hyperplasia of airway smooth muscle, increases in goblet cell number, enlargement of sub-mucous glands and remodelling of the airway connective tissue. In susceptible individuals these inflammatory changes result in the well known signs and symptoms of asthma such as wheezing, breathlessness, chest tightness and cough, which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Inhaled corticosteroids (ICSs) are the cornerstone of modern asthma treatment. They control the underlying airway inflammation in asthma by inhibiting many aspects of the inflammatory process, such as inhibiting the release of inflammatory mediators and cytokines from a wide range of inflammatory cells, reducing the expression of adhesion molecules, reducing the survival of inflammatory cells and increasing the synthesis of anti-inflammatory proteins. Additionally, corticosteroids can increase the expression of $\beta_2$-adrenoceptors and decrease the transcription of genes coding for inflammatory receptors.

The aim of the present article was to review the Global INitiative for Asthma (GINA) guidelines on what constitutes asthma control, assess the current status of asthma control and discuss the many reasons why asthma, despite many pharmacological and technological advancements, remains a poorly controlled disease.

**Asthma control**

Both national and international asthma management guidelines are now widely available. Their principle aim is to achieve control of the disease, but what exactly constitutes asthma control? According to the GINA guidelines asthma is controlled if patients have: minimal chronic symptoms (including nocturnal symptoms); minimal or infrequent exacerbations of their asthma; no emergency hospital visits; minimal (ideally no) use of as needed $\beta_2$-agonists; no limitation to their activity levels (including exercise); peak expiratory flow rate (PEF) circadian variation <20%; near normal PEF and; minimal (or no) adverse effects from medication. These guidelines are updated every year ensuring that they are always up to date, so providing the best possible advice on asthma management. The premise of the GINA approach to therapy is to achieve control of asthma with the least possible medication. As asthma severity increases the dose of ICSs are stepped up and other classes of drugs are added, particularly long-acting $\beta_2$-agonists (LABAs). Once control of asthma has been achieved and maintained for at least three months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy needed to maintain control.

However, despite the implementation of asthma management guidelines around the world, and the availability of highly effective medication to combat asthma symptoms and the underlying inflammatory component of the disease, asthma remains poorly controlled. A survey by Rabé and colleagues showed that of 2803 asthmatic patients in the Asthma Insights and Reality in Europe (AIRE) study, 46% reported daytime symptoms and 30% reported asthma-related sleep disturbances, at least once a week. Additionally, in the previous 12 months, 25% of patients reported an unscheduled urgent care visit, 10% reported one or more emergency room visits, 7% reported overnight hospitalisation due to asthma and 17% reported taking time off work due to their asthma symptoms. In the US the situation was even worse (Fig. 1). This lack of control may be due to the fact that patients are not being prescribed the recommend medication, and if they are, they are not taking it. The same study by Rabé and colleagues showed, not surprisingly, that patients with mild asthma used short-acting $\beta_2$-agonists (SABAs) more than ICSs. But, what is shocking is the fact that this same treatment pattern was found in moderate asthma and even in severe asthma, where less than one-third of patients were taking ICSs (Fig. 2). This statistic is extremely worrying, bearing in mind
that ICS therapy could control the majority of these patients. Patients attending their general practitioner are also poorly controlled. A study by Gruffydd-Jones showed that a high proportion of patients (approximately 50%) with typical symptoms of asthma complained of wheezing, chest tightness, cough and breathlessness (Fig. 3), which significantly impacted on their lifestyle and activities (Fig. 4). Even patients who felt well were symptomatic, showing that patients underestimate their own symptoms and provide evidence that asthma control may be even worse than previously thought (Fig. 3). All aspects of lifestyle were affected including sleep, playing sport, going up and down stairs, walking, socialising, playing with children, going to work and sex life (Fig. 4). Bearing in mind the degree of lifestyle restrictions these patients were experiencing, it was very surprising that few of them discussed it with their doctor or specialist nurse (Fig. 4). These results show that poor control of asthma is a huge unrecognised problem.

Why is asthma poorly controlled?

Asthma management guidelines provide recommendations for the optimal control of asthma. It follows that one reason why asthma remains poorly controlled may be that the guidelines are not being implemented. Not only are physicians and patients not adhering to asthma management guidelines, but the guidelines themselves suffer from inherent limitations. The generic nature of the guidelines is an advantage on the one hand, but they cannot take account of individual differences in response to treatment and severity of side effects, neither can they take account of the availability and/or cost of pharmacological treatments in different countries. Even without this information the guidelines are long which may not be conducive to rapid understanding and incorporation into busy treatment schedules. Although the guideline recommendations are based on the best available scientific evidence, including randomised controlled trials, systematic reviews and meta-analyses, each of these types of study have disadvantages associated with them. The clinical studies usually have a double-blind, placebo-controlled design and include very carefully selected patients who are usually compliant with therapy and instructed in the use of inhalers. In the ‘real world’ things are very different and patients frequently fail to understand how to use their therapy and are often non-compliant. The current lack of asthma control as reported by patients in the AIRE study partly reflects the extent to which guidelines are not being implemented.

The GINA guidelines recognise patient non-compliance with therapy as a major reason why
asthma remains poorly controlled. Reasons for non-compliance are complex and may be split into drug and non-drug factors. Drug factors include: difficulty using the inhaler device; complicated treatment regimens; side effects of treatment; cost; the fact that people do not like taking treatment; or that the treatment is not readily available. Non-drug factors are also barriers to compliance and include such issues as: not understanding the instructions; worrying about side effects; not trusting the doctor; not being supervised taking medication so compliance is never checked; and anger about being ill. There are also cultural issues such as patients do not like being labelled with the disease, they may forget to take the treatment and there may be religious or ethical difficulties.

It is essential that when a given inhaled therapy is prescribed to the patient that thought is given to the inhalation device that delivers the drug to the lung. In order to successfully deliver drug to the lungs patients need to both understand how to deliver the drug and need to be comfortable with the delivery device. Inability to correctly use inhaler devices is a major reason for non-compliance with therapy. Pressurised metered dose inhalers (pMDIs) are the most frequently prescribed inhaler device but most patients cannot use them effectively. Misuse of pMDIs, which is mainly due to poor co-ordination between inhaler activation and inhalation, is frequent and associated with poorer asthma control in ICS-treated patients. Dry powder inhalers (DPIs) have several advantages over MDIs. They are breath-activated, easy and convenient to use and environmentally friendly.

In summary, asthma management can be summarised as a triangular relationship between the patient, drug treatment and delivery device, with each of these components interacting with the other (Fig. 5). Asthma management guidelines recommend the appropriate drug treatment for patients based upon the severity of their disease. The choice of delivery device is equally as important as choice of therapeutic agent as the amount of drug delivered to the lungs differs from device to device. Device choice should also be governed by patient choice as well as ease of use and consistency of drug release which all have implications for patient compliance. However, patients are frequently non-compliant with their therapy due in part to non-implementation and non-adherence to asthma management guidelines and also to misuse of inhaler devices.

Conclusions

There are now several other delivery devices besides pMDIs on the market, including breath-
activated pressurised inhalers and DPIs that are much easier for patients to use. These devices require less instruction, are easier to use and deliver drug efficiently which results in better lung deposition of the inhaled drug. More ‘real world’ studies are needed in which patients are not selected according to strict inclusion or exclusion criteria, but reflect the range of patients normally seen in clinical practice. "N of 1" studies are also useful for determining how individual patients respond to different treatments and this might include different drugs as well as different types of inhaler. There is no doubt that the type of inhaler is just as important as the class of drug in the long-term management of asthma in adults and children. Although there are several new treatments for asthma, which may be given orally (more specific drugs) or via injection (monoclonal antibodies), it is unlikely that these will be as effective as ICSs or LABAs, so that inhaled therapy is likely to remain predominant in the future. Improvements in inhaled drug delivery will therefore continue to be paramount in improving asthma management.

References