Asthma is a common disease that leads to significant degrees of morbidity and mortality. It is characterised pathologically by a lymphocytic and eosinophilic infiltration of the bronchial tree with associated airway narrowing. Physiologically it is characterised by bronchial hyper-reactivity and, clinically, by variable degrees of chest tightness, wheeze, cough and shortness of breath.

The incidence of asthma appears to be increasing especially in developed countries with up to 10 per cent of the population affected which may be linked to the increasing prevalence of atopy. Asthma is thought to be the clinical manifestation of an inappropriate response of a previously sensitised airway to an allergen. The majority of asthmatics are also atopic, although a significant proportion (10–20 per cent) are not. However, the immunopathological changes seen in non-atopic (intrinsic) asthma are similar to those seen in atopic (extrinsic) asthma suggesting that the underlying mechanisms are similar.

The management of asthma involves both pharmacological and non-pharmacological interventions. Non-pharmacological interventions include appropriate management of often undetected contributing disease (eg, bronchiectasis), avoidance of known precipitating factors, and specific allergen avoidance. Patient education about the disease is of paramount importance although, sadly, it is often neglected.

This review will concentrate on the management of chronic asthma in adults and discusses both current and potential future therapies. The treatment of acute asthma in adults and asthma in children are not covered in this article.

The management of asthma depends on the severity of the disease, as well as the nature and frequency of the attacks. The British Thoracic Society (BTS) guidelines provide a classification of asthma severity. A summary can be found in Figure 1 (p242). Treatment should be started on a step higher than clinically indicated and stepped down once control has been achieved. It is essential to follow up the patient to determine whether the current treatment is adequate.

In the past decade, asthma treatment has emphasised long-term inflammatory suppression with corticosteroids and symptomatic relief with short-acting bronchodilators. Additional treatment, with long-acting β2-receptor agonists, theophylline, cromones and leukotriene antagonists, has been shown to help in controlling asthma.

Both new and established drugs for treating asthma are covered in this article. There is also a discussion of the various inhaler devices.
ß2-receptor agonists (eg, salmeterol and formoterol) are indicated for regular use (twice daily in the BTS guidelines) in conjunction with low-dose inhaled steroids. They are used to control symptoms and reduce frequency of exacerbations.5

Long acting ß2-receptor agonists Long-acting ß2-receptor agonists (eg, salmeterol and formoterol) are indicated for regular use (twice daily in the BTS guidelines) in conjunction with low-dose inhaled steroids. They are used to control symptoms and reduce frequency of exacerbations. Formoterol has been licensed for additional “reliever” doses (up to a maximum dose of 72µg per day). This use, however, is not recommended in the current guidelines.

Tolerance Tolerance to ß2-receptor agonists may occur in some patients as a result of regular use, and is more pronounced for the bronchoprotective effects than the bronchodilator action.1,5

Antimuscarinics (ipratropium and oxitropium) are specific antagonists to muscarinic receptors. They inhibit reflex cholinergic-induced bronchoconstriction. The effects of histamine and leukotrienes on bronchial smooth muscle are not inhibited by antimuscarinics.1 Antimuscarinics are generally less effective than ß2-receptor agonists in patients with asthma, although they have a longer duration of action. They are reserved for use mainly in severe acute exacerbations and in patients who suffer from tremor or palpitations with ß2-receptor agonists.3

Long-acting antimuscarinics can also be used in patients whose asthma is not adequately controlled with ß2-receptor agonists alone, and as regular maintenance bronchodilator therapy in patients requiring high-dose inhaled steroids. Their use is indicated in step 4 of the BTS guidelines. They can also be used to treat nocturnal asthma which may be caused by increased cholinergic tone in asthmatic airways. Panel 1 (p243) shows some adverse effects of antimuscarinics.

Table: Adverse effects of short-acting ß2-receptor agonists

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle tremor</td>
<td>Stimulation of ß2-receptors in skeletal muscle</td>
</tr>
<tr>
<td>Tachycardia and palpitations</td>
<td>Reflex cardiac stimulation secondary to peripheral vasodilation. Direct stimulation of atrial ß2-receptors and possibly stimulation of myocardial ß1-receptors as doses of ß2-receptor agonists are increased</td>
</tr>
<tr>
<td>Metabolic effects</td>
<td>Seen with large systemic doses (increase in free fatty acids, glucose and insulin)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>ß2-Receptor stimulation of potassium entry into skeletal muscle</td>
</tr>
</tbody>
</table>

Theophylline The bronchodilatory effect of theophylline has been used for many years in the management of patients with persistent symptoms. Theophylline is indicated in step 4 of the BTS Guidelines as an additional bronchodilator to ß2-receptor agonists in patients taking high-dose (800µg–2,000µg daily) inhaled steroids whose asthma is still uncontrolled. In patients unable to tolerate high-dose inhaled steroids, theophylline may be prescribed as additional therapy to low-dose inhaled steroids (step 3 of the BTS guidelines). Patients who suffer from nocturnal asthma may benefit from slow release preparations of theophylline as these can provide therapeutic plasma concentrations overnight.

Theophylline is a non-selective inhibitor of phosphodiesterase, the enzyme that degrades cyclic-3,5-adenosine monophosphate (cAMP), of which there are seven isoenzymes. This results in increased levels of intracellular cAMP and therefore bronchodilation. It is the inhibition of phosphodiesterase-3 and -4 isoenzymes in particular which is believed to result in airway smooth muscle relaxation.4

Recently, theophylline has been shown to have an anti-inflammatory or immunomodulatory effect when lower doses are used to produce serum concentrations of less than 10mg per litre.7 It may therefore be of benefit when used in combination with inhaled steroids. Inflammatory cells, such as eosinophils and T-lymphocytes, contain several phosphodiesterase enzymes and the anti-inflammatory effect of theophylline is believed to be due to its action on the phosphodiesterase-4 isoenzyme. This has led to new phosphodiesterase inhibitors being developed which have been suggested to have a greater anti-inflammatory effect than theophylline, because of their greater selectivity of phosphodiesterase-4 (PDE4).

The addition of regular theophylline to the regimen of patients on low-dose inhaled corticosteroids may provide a useful alternative to increasing the dosage of corticosteroids in suitable patients. A randomised study comparing the use of high-dose inhaled budesonide (1,600µg daily) and low-dose budesonide (400µg daily) plus low-dose theophylline (producing plasma concentration of 10mg per litre) in patients with moderate asthma, showed improvement in lung function with both regimes, but a greater effect was observed with low dose budesonide plus theophylline.9,10 However, the anti-inflammatory effect of theophylline in asthma still needs to be defined.

Due to the adverse effects (see Panel 2, p243), risk of toxicity, requirement for regular monitoring of serum concentrations, and evidence to show that ß2-receptor agonists are more effective bronchodilators, the use of theophylline as a bronchodilator has decreased. In a comparison between oral theophylline and inhaled salmeterol in patients with moderate to severe asthma, salmeterol was shown to be more effective at producing bronchodilation and symptomatic relief.6,10

Corticosteroids Corticosteroids are the most effective treatment for asthma and inhaled thera-
Increasing the dose of inhaled corticosteroids could improve lung function. However, the addition of corticosteroid was more effective at preventing severe exacerbations than the addition of formoterol. A meta-analysis which compared the addition of salmeterol to inhaled corticosteroids with an increase in the dose of inhaled corticosteroids showed that the addition of salmeterol was associated with improvements in lung function and symptom scores and a reduction in the need for rescue medication.

In conclusion, the addition of a long-acting β2-receptor agonist is probably recommended for those with persistent symptoms whereas for those patients suffering repeated severe exacerbations, an increase in the dose of inhaled corticosteroids would be more beneficial.

### Prophylactic agents

The UK, cromones and leukotriene receptor antagonists are used in the prophylaxis of asthma.

Cromones are used as additional therapy at steps 3 and 4 of the BTS guidelines, but in clinical practice are rarely used as add-on therapy. The exact mechanism of action of the cromones is not fully understood. They are known to inhibit the release of mediators from mast cells by causing mast cell stabilisation, and are therefore referred to as mast cell stabilisers. Cromones have recently been shown to have an inhibitory effect on several inflammatory cells such as eosinophils, neutrophils and macrophages, and may act on chloride channels found in mast cells and other inflammatory cells. Both cromoglicate and nedocromil reduce allergen-induced early and late phase reactions, and inhibit bronchospasm during and after exercise and exposure to cold or dry air. They tend to be more effective in patients with mild atopic asthma, in particular children with exercise- or allergen-induced asthma. It is still not clear why the cromones are most effective in allergic asthma.

Because of their short duration of action and four-times-daily dosing, compliance with therapy can be a problem. However, cromones are well tolerated and rarely cause adverse effects (see Panel 3).

Leukotriene receptor antagonists Cysteinyl leukotrienes, including leukotrienes C4, D4 and E4 are endogenous molecules synthesised from arachidonic acid, which is present in most of the body’s cells. Their role in the pathogenesis of asthma is to cause potent stimulations of bronchial smooth muscle, causing the release of eosinophils and production of secretions in the airways. The development of the leukotriene receptor antagonists (LTRA) produced the first new licensed treatment for asthma in 30 years. They have been described as a “hybrid” treatment because of their potential to relieve smooth muscle bronchoconstriction without affecting the action of short-acting β2-receptor agonists as well as preventing inflammation. Currently, there are two LTRAs licensed for the treatment of asthma in the UK, montelukast and zafirlukast. They are indicated for the prophylaxis of asthma and should be considered add-on therapy and not used to relieve an attack of severe asthma.

Studies comparingLTRAs with placebo in mild to moderate asthma have demonstrated that they can improve lung function by 10–15 per cent. They also reduce symptoms and night-time wakening, reduce rescue medication use, days off work or school, exacerbation rates, and improve quality of life. Furthermore, LTRAs are effective inhibitors of the early and late phase asthmatic response, aspirin-sensitive asthma and exercise-induced asthma. They can also reduce eosinophils, denoting a reduction of the inflammatory response.

In a trial by Malmstrom et al., 895 patients with chronic asthma with lung function ranging between 50–85 per cent (predicted) and at least 15 per cent bronchodilator reversibility, were randomised to receive montelukast 10mg and beclometasone 200µg (inhaled via a large volume spacer) or placebo. The results showed that both montelukast and inhaled beclometasone were more effective than placebo. Beclometasone was significantly more effective in all outcome measures than montelukast, although the clinical benefit gained from montelukast was significantly faster than inhaled corticosteroids. The use of an LTRA combined with inhaled corticosteroids has been shown to be more effective than monotherapy. However, addition of montelukast to therapy in patients with moderate to severe asthma did not gain the same benefit as in those with mild asthma.
not provide any additional improvement in terms of lung function and symptom scores in this group.29

A study on the effect of LTRA on asthma exacerbation has shown a reduction in attacks.30 This has been confirmed in a recent meta-analysis of zafirlukast, which showed that the drug reduces exacerbation rates to half that of patients on placebo.31

The most familiar and commonly prescribed device in the UK is the pMDI. Within the pressurised canister, the drug is dissolved or suspended in a propellant. When the device is activated, one metered dose of drug mixed with propellant is released.32 Traditionally, the pMDI contained chlorofluorocarbon (CFC) propellants to release the drug. However, these propellants are being phased out because of their harmful effects on the ozone layer. The cost of changing the propellants to hydrofluoroalkane (HFA) compounds is extremely high and it has been suggested that these new compounds may harm the environment and may also be phased out in time. In spite of this, CFC-free devices are becoming more widespread.

The advantages of pMDIs are that they are lightweight, portable, contain many doses, are available in a wide range of treatments and are inexpensive. However, there is one major disadvantage: in order to achieve maximum benefit, precise co-ordination between activation of the device and inhalation of the drug is essential. This manoeuvre is an important element for achieving good lung deposition, which has been estimated at between 7–20 per cent.33

To overcome the problem of co-ordination, a spacer device can be used which acts as a holding chamber from which the drug can be inhaled, and also reduces local and systemic side effects.35 Spacer devices are useful for delivering high doses of treatment, and increase the amount of drug deposited in the lungs by around 50 per cent.35 Unfortunately, the early devices are bulky and are often impractical for patients. Smaller devices, such as the Aerochamber and Able spacer are now available.

The breath-actuated device (BAD) also eliminates the problem of co-ordination with pMDIs and is suitable for all ages, except infants. The amount of drug deposited in the lungs is approximately that of the pMDI if used correctly every time. Lenney et al36 compared seven different devices and found that BAds were consistently used correctly as well as being the device most preferred by patients.

Dry powder inhalers (DPIs) are breath-operated and dependent on inspiratory effort. These devices are portable, CFC-free, and easy to use.33 As these devices are dependant on inspiratory effort so is the amount of drug deposited in the lungs, which has been estimated to range between 10–35 per cent34 with the turbohaler having probably the best deposition.37

### Panel 4: Adverse effects of LTRAs

<table>
<thead>
<tr>
<th>Headache</th>
<th>Dizziness</th>
<th>Hypersensitivity reactions</th>
<th>Dry mouth</th>
<th>Churg-Strauss syndrome</th>
<th>Restlessness</th>
<th>Sleep disorders</th>
</tr>
</thead>
</table>

Leukotriene receptor antagonists have yet to be incorporated into the BTS guidelines for asthma management. It would appear from clinical trials that certain groups of patients, for example, exercise-induced asthmatics, might respond to these therapies, but since inhaled corticosteroids are the mainstay of preventive treatment of asthma in the UK, the impact of LTRAs may only be minor.

### Drug delivery devices

The main treatments for asthma are administered by inhalation. This route is preferred because it ensures that the drug can be delivered directly to its site of action in the lungs and airways, thus encouraging maximum efficacy. Also, the smallest therapeutic dose can be given, thus minimising the risk of side effects.3 Inhale devices include the pressurised metered dose inhaler (pMDI), dry powder inhaler (DPI) and nebulisers.

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### NEW TREATMENTS

As a result of the increased understanding of the pathophysiology of asthma, new treatments are being developed which act on specific areas of the inflammatory cascade. These include anti-immunoglobulin E (IgE) therapy, phosphodiesterase-4 inhibitors, peptide-based immunotherapy, as well as anti-interleukin (IL)-4 and anti-IL-5 therapy.

Omalizumab Omalizumab is a recombinant monoclonal antibody specific to IgE. In patients with allergic asthma, raised levels of IgE are usually found, and it is the overproduction of this antibody that leads to activation of the inflammatory response. The severity of asthma symptoms and airway hyper-responsiveness correlates to the number of circulating IgE.38 During an allergic response, B cells become activated and are stimulated by IL-4 and IL-13 (produced by T helper cells) to differentiate and produce IgE. This in turn binds to receptors on both mast cells and basophils, thereby triggering the release of inflammatory mediators which produce the early and late phase responses such as bronchoconstriction.39

Omalizumab works by binding to free, but not bound serum IgE released in response to exposure to allergens. This prevents IgE from binding to the high affinity Fc epsilon RI receptor (FceRI) exposed on the surface of both mast cells and basophils, and therefore the consequent release of inflammatory mediators is inhibited. Omalizumab also causes the down regulation of the surface high affinity receptors.

Studies have shown a dose-dependent decrease in free serum IgE levels following the administration of omalizumab, which...
correlates with improvements in clinical outcomes. Randomised double blind trials have shown a reduction in the early and late phase response to inhaled allergens and a reduction of sputum eosinophil counts in patients with allergic asthma.

Omalizumab was found to cause a reduction in mean asthma symptom scores, inhaled steroid dose, and asthma exacerbations in a placebo-controlled trial involving 317 patients. A phase III trial involving 525 patients who were randomised to receive subcutaneous omalizumab 150–300mg every four weeks, subcutaneous omalizumab 225–375mg every two weeks or placebo, was carried out for 28 weeks. Patients were monitored for asthma exacerbations in two phases, a 16-week stabilisation phase and a 12-week corticosteroid reduction phase. A significant reduction in exacerbations was observed with omalizumab in comparison with placebo.

Trials to date have shown that omalizumab produces beneficial effects in patients, but further trials and clinical experience are required before its place in therapy can be determined. It is likely that omalizumab will fit into steps 4 or 5 of the BTS Guidelines, but will be reserved for patients with severe allergic asthma uncontrolled by existing therapy.

Panel 5: Action of PDE4 inhibitors

<table>
<thead>
<tr>
<th>Relax airway smooth muscle</th>
<th>Decrease bronchoconstriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce secretion of inflammatory mediators, such as histamine, leukotrienes, cytokines and chemokines (GM-CSF, IL-4, IL-5, eotaxin)</td>
<td>Block leucocyte adhesion to vascular endothelial cells</td>
</tr>
<tr>
<td>Block generation of oxygen-derived free radicals</td>
<td>Block generation of oxygen-derived free radicals</td>
</tr>
</tbody>
</table>

Panel 5 lists the actions of PDE4 inhibitors. Selective PDE4 inhibitors suppress many processes believed to contribute to the inflammation associated with asthma by blocking cAMP degradation, and have been developed with the aim of reducing the adverse effects profile associated with non-selective inhibitors such as theophylline. PDE4 inhibitors may improve the airflow obstruction seen in asthmatic patients because they reverse or prevent bronchoconstriction, limit airway oedema and potentially alter mucus secretion and clearance. They are able to suppress the activity of inflammatory cells, as well as inhibiting cytokine production (IL-2, IL-4 and IL-5). Cytokine production is involved in maturation and recruitment of T cells and eosinophils as well as production and release of pro-inflammatory cytokines and chemokines such as TNF-a and interferon gamma. Selective PDE4 inhibitors reduce or abolish the migration of eosinophils and neutrophils in the lung in response to antigen, lipopolysaccharides, lipid mediators and histamine.

Cilomilast (Ariflo) is a second generation PDE4 inhibitor which has anti-inflammatory actions. It is reported to produce a greater effect on FEV1 than salmeterol and suppresses early and late phase responses to allergens in asthmatic subjects. Trials in patients with chronic obstructive pulmonary disease suggest it may be effective maintenance treatment.

Peptide-based immunotherapy As described above, asthma is usually induced following exposure to an allergen. In some instances, asthma is predominantly driven by a single allergen, e.g., grass pollen or cat dander. Traditional immunotherapy has been shown to be effective but carries the risk of anaphylaxis. This suggests that peptide-based immunotherapy may provide a safer alternative in the future because the short peptides used are theoretically not long enough to cross-link IgE and thus cannot induce an early allergic reaction.

A number of studies to date have assessed the use of peptides derived from cat dander in the treatment of cat-allergic asthma. These in vitro findings were accompanied by a reduction in the allergic response in the skin, suggesting a potential role for allergen-derived peptides in the treatment of allergic disease. Importantly, no subject developed an early allergic reaction following administration of the peptides, implying that IgE-cross-linking was not occurring with the shorter peptides. Evidence for peptide-based immunotherapy for allergic disease and asthma remains preliminary and needs confirmation in larger studies but is currently encouraging and may provide an option in some cases of mono-allergic asthma.

Anti-IL-4 IL-4 is produced by allergen-specific T lymphocytes following activation and helps to promote the allergic phenotype. Consequently, inhibition of IL-4 at a functional level is potentially a mechanism for down-regulating the allergic reaction. Borish et al recruited 25 moderate atopic asthmatic patients into a double blind placebo controlled study of altraksincept, the soluble extracellular portion of the high affinity receptor for IL-4. The subjects were randomised to receive either placebo, low-dose (500mg) or high-dose (1,500mg) anti-IL-4.

Treatment with high-dose anti-IL-4 was associated with a significant reduction in total asthma symptom scores and beta2-receptor agonist use when compared with placebo and low dose anti-IL-4. No differences were seen in the morning or evening peak expiratory flow rates although there were significant differences in FEV1 in the high dose group. Bronchial hyper-reactivity as assessed by methacholine challenge was decreased in the high dose group. Treatment with placebo and low-dose anti-IL-4 was associated with a gradual rise in exhaled nitric oxide, suggesting an increase in airway inflammation. Levels in the high-dose group...
declined to levels significantly lower than placebo.

Treatment with anti-IL-4 was well tolerated. There were no serious adverse events and no subject developed antibodies against anti-IL-4. Importantly, no subject in the high-dose group had to withdraw from the study because of an asthma exacerbation. However, three out of eight in the low-dose group and two out of eight in the placebo group withdrew.

As with IL-4, IL-5 is an important mediator in the allergic response. It is the major factor controlling the terminal differentiation of eosinophils, and increased levels of IL-5 can be demonstrated in both serum and bronchial biopsies from asthmatic subjects. The late allergic reaction, which acts as a model of chronic inflammation, is associated with increased serum IL-5 and eosinophils. Additionally, inhaled IL-5 is associated with airway hyper-reactivity and sputum eosinophilia. Consequently, inhibition of IL-5 can be demonstrated in both serum and bronchial biopsies from asthmatic subjects. The choice of inhaler device should be made on an individual patient basis with the device which the patient finds easiest to use and demonstrates good inhaler technique being chosen.

There is little evidence to support the fact that allowing the patient to choose their device increases compliance, but providing information on each device encourages the patient to make an informed choice and to become actively involved in their own management. Both physical and cognitive ability must be considered. For example, the elderly may have difficulty in assembling the pMDI and spacer, whereas using the DPI may cause irritation and coughing on inspiration, thus reducing the amount of drug deposited in the lungs.

With the change over of inhaler devices to CFC-free formulations that differ in their taste and characteristics, patients will need to be made aware of the changes and reassured about the continued efficacy of their medicines. Finally, patients should be seen regularly, and have their medication and inhaler technique reviewed on a regular basis.

## SUMMARY

The understanding of the mechanisms of asthma has increased dramatically through research. This has led to the development of new therapies which specifically target particular inflammatory mediators, all of which will further improve the outcome of patients with asthma.

## ACKNOWLEDGEMENTS

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## REFERENCES


