Key points

- Although treatment guidelines for both asthma and chronic obstructive pulmonary disease (COPD) follow a stepwise, severity-based approach, and share a repertoire of drugs, they have different characteristics. While asthma treatment focuses on inflammation, COPD therapy is symptom-focused.
- Asthmatics generally respond better than COPD patients to bronchodilators, but the differences are not necessarily clear-cut – the way in which patients respond is more informative about their disease than whether they respond.
- While the use of inhaled corticosteroids (ICS) as a first-line therapy in asthma is uncontroversial and backed by a substantial body of evidence, their value in COPD may be restricted to particular phenotypes of the disease.
- Combination therapy with ICS and long-acting β_2-agonist (LABA) is the preferred treatment when medium-dose ICS alone does not achieve asthma control. In COPD, combination therapy has been beneficial in many patients, but the heterogeneity of the disease complicates the picture.

Current opinion: Pharmacological approaches in asthma and COPD

Educational aims

- To illustrate the similarities and differences in the treatment of asthma and COPD.
- To explain whether the response to bronchodilators in asthma and COPD predicts prognosis and response to other interventions.
- To assist in therapeutic choices for asthmatic and COPD patients.

Summary

Bronchodilators, inhaled corticosteroids and other anti-inflammatory agents form the basis of treatment to control the symptoms and progression of asthma and COPD. However, although the armoury of medications used for the two conditions is largely similar, the goals and targets of therapy are different. In fact, owing to their different mechanisms of development, the two diseases are regarded quite differently. Therefore, the two require different pharmacological treatments. In general, therapy for asthma is targeted at reducing inflammation, whereas for COPD it is directed at relief of symptoms. In this article, the pharmacological treatment of asthma and COPD, based on recently updated guidelines, is described.

There are now many guidelines that provide direction for the diagnosis and management of asthma and chronic obstructive pulmonary disease (COPD) [1–4]. Asthma treatment guidelines aim to ensure that control is gained and maintained using a stepwise approach, tailoring treatment both to the severity of the asthma and to the individual day-to-day needs of the patient, while employing the lowest effective medication dose. Current COPD guidelines also advocate a stepwise approach to treatment based on disease severity, with more focus on preventing disease progression; but while treatment of asthma is characterised by suppression of inflammation, treatment of COPD is characterised by relief of symptoms.

The goals of therapy in asthma are thus different from those in COPD [5] (table 1). The goals of long-term management of asthma should include the following:

1) Achievement and maintenance of control of symptoms;
2) Prevention of asthma exacerbations;
3) Maintenance of pulmonary function as close to normal levels as possible;
4) Maintenance of normal activity levels, including exercise;
5) Avoidance of adverse effects from asthma medications;
6) Prevention of the development of irreversible airflow limitation;
7) Prevention of asthma mortality.

The treatment goals for COPD are:

1) The prevention of disease progression;
2) The relief of symptoms;
3) Improvement in exercise tolerance;
4) Improvement in health status;
5) Prevention and treatment of exacerbations;
6) Prevention and treatment of complications;
7) A reduction in mortality;
8) Minimisation of side-effects from treatment.

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Table 1 Goals of therapy in asthma and COPD

Asthma	COPD
Achieve normal lung function	Prevent disease progression
No symptoms	Relieve symptoms
Maintain normal quality of life	Improve exercise tolerance
Prevent and treat exacerbations	Improve health status
Prevent mortality	Prevent and treat complications
	Prevent and treat exacerbations
	Reduce mortality

Bronchodilators, inhaled corticosteroids (ICS) and other anti-inflammatory agents form the basis of treatment to control the symptoms and progression of asthma and COPD. However, although the armoury of medications used for the two conditions is largely similar (table 2), the goals and targets of therapy are different. Choice of treatment differs significantly between asthma and COPD because, as mentioned above, therapy for asthma is targeted at reducing inflammation, whereas for COPD is directed at relief of symptoms.

The discovery of airway inflammation as a major pathophysiological component of asthma has led to the use of ICS as the mainstay of asthma therapy. Many patients need additional drug therapy, typically bronchodilators that relax airway smooth muscle, for the relief of acute symptoms. Additionally, sustained improvements in lung function may be achieved with the regular use of long-acting bronchodilators. This is also true in COPD.

Bronchodilators

Bronchodilators cause immediate reversal of airway obstruction as a result of an effect on airway smooth muscle; other pharmacological effects on other airway cells (reduced microvascular leakage, reduced release of bronchoconstrictor mediators from inflammatory cells) may contribute to the reduction in airway narrowing.

Bronchodilators can be categorised as either short acting (~4 h duration) or long acting (>12 h duration). Currently, two main types of bronchodilators are in clinical use: β_2-agonists (which stimulate the β-adrenoceptor, increasing cAMP concentration and resulting in airway smooth-muscle relaxation) and muscarinic acetylcholine (ACh) receptor antagonists, which antagonise the constricting effect of ACh on airway smooth muscle [6]. Both types of bronchodilator provide effective symptomatic relief and are currently the first-line therapy of choice for the treatment of airway constriction.

In general, patients with asthma typically show a large bronchodilator response to β_2-agonists. By contrast, patients with COPD usually have a poor bronchodilator response, although there is significant evidence that a component of the airway obstruction in COPD is partially reversible and responsive to bronchodilators [3, 4]. Table 3 highlights the different profiles of bronchodilators in asthma and COPD.

In an attempt to differentiate the use of bronchodilators in asthma from that in COPD, we must address some fundamental questions (table 4). First of all, we should clarify definitively whether revers-

Table 2 Medications for asthma and COPD

Asthma	COPD
Anti-inflammatory drugs	**Bronchodilators**
Corticosteroids	Short- and long-acting β_2-agonists
Antileukotrienes	Short- and long-acting anticholinergics
Cromones	Theophylline
Theophylline (?)	**Anti-inflammatory drugs**
Bronchodilators	Corticosteroids
Short- and long-acting β_2-agonists	**ICS/long-acting β_2-agonist combination**
Short-acting anticholinergics	**Mucoactive drugs**
ICS/long-acting β_2-agonist combination	**Antibiotics**
Anti-immunoglobulin E	**Vaccination**

Table 3 Different profiles of bronchodilators in asthma and COPD

Asthma	COPD
Short-acting β_2-agonists	**Short-acting β_2-agonists**
Tolerance	No tolerance
Dosed as needed	Regularly dosed
Long-acting β_2-agonists	**Long-acting β_2-agonists**
Monotherapy associated with increased frequency of exacerbations	Monotherapy associated with decreased frequency of exacerbations
Little tolerance	Little tolerance
Anticholinergics	**Anticholinergics**
Efficacious in acute attack	Efficacious in acute and stable disease

ibility to bronchodilators discriminates between asthma and COPD, or whether the two represent a continuum. We should determine whether asthmatics and patients with COPD respond similarly in terms of changes in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) and react selectively to different bronchodilators. This is a critical point, because it should enable us to predict which type of inhaled bronchodilator – an antimuscarinic drug or a β_2-agonist – is more efficacious in long term treatment of asthma or COPD. We should also establish the real advantage in combining bronchodilators with different mechanisms of action.

Does reversibility to bronchodilators differ between asthma and COPD?

The presence or absence of reversibility [7] was once thought to be the major distinction between asthma and COPD, with reversibility of airflow obstruction being the hallmark of asthma, and mainly irreversible obstruction that of COPD. The problem is that even asthmatic patients, particularly those suffering from more severe asthma, can demonstrate a component of fixed obstruction. Indeed, fixed obstruction has been reported to occur in 30% of a large population of patients with the diagnosis of asthma [8]. Likewise, considerable reversibility of lung function exists in patients with a diagnosis of COPD. Using 15% improvement in FEV_1 as the threshold to distinguish between asthma and COPD, Mannino *et al.* [9] found it afforded only 44% sensitivity for detecting asthma, and a quite modest 72% specificity in distinguishing asthma from COPD.

Apparently, the acute responses of FEV_1 and FVC following a standard dose of inhaled bronchodilator are neither sufficiently sensitive nor sufficiently specific to differentiate asthma from COPD purely on spirometric grounds [8]. Moreover, sensitivity for the diagnosis of asthma is highest for those with the most severe reductions in FEV_1. Neither residual volume (RV) nor total lung capacity (TLC) reflects degrees of airflow limitation as well as does the RV/TLC ratio [8].

There is evidence that a ΔFEV_1 ≥0.2 L gives the most satisfactory combination of sensitivity and specificity and the highest positive and negative predictive values for diagnosing asthma [10]. These values are superior to those obtained using the European Respiratory Society (ERS) or the American Thoracic Society (ATS) criteria for reversibility (ΔFEV_1 ≥9% predicted or ΔFEV_1 of ≥12% pred and 0.2 L over baseline, respectively) [10]. Expressions of response in terms of changes in FVC are unsatisfactory in separating the two diseases [10].

It should be pointed out that 23–42% of COPD patients are responsive to bronchodilator, depending on the criteria used [11]; moreover, bronchodilator responsiveness is a continuous variable [11]. Overall, 52% of patients classified by ATS criteria and 253 out of 660 (38%) classified using ERS criteria would be reclassified if tested on a different occasion [11].

Do asthmatics and patients with COPD respond similarly in terms of changes in FEV_1 and FVC?

Patients with asthma more frequently increase their FEV_1 by >200 mL, and most show an

Table 4 Questions to be addressed for differentiating the use of bronchodilators in asthma from that in COPD

- Does reversibility to bronchodilators discriminate between asthma and COPD, or do the two represent a continuum?
- Do asthmatics and patients with COPD respond similarly in terms of changes in FEV_1 and FVC?
- Do patients with asthma and COPD react selectively to different bronchodilators?
- Which type of inhaled bronchodilator is most efficacious in long-term treatment of asthma or COPD?
- What is the genuine advantage in combining bronchodilators with different mechanisms of action?

increase in FEV_1 alone or in both FVC and FEV_1 [12]. On the contrary, in COPD, an FVC response alone is most common. An isolated FEV_1 increase is noted only rarely in COPD. Younger patients have an increase primarily in FEV_1 or in both FEV_1 and FVC [12].

After 400 µg salbutamol inhalation, both asthmatic and COPD patients show an increase in all flow–volume curve parameters [13]. Usually, mean responses are significantly greater in the asthma group for all FEV_1 criteria. Absolute changes in FVC after bronchodilator administration are significantly greater in asthma subjects in comparison to COPD patients. The forced expiratory flow when 50% of FVC has been exhaled (FEF50) shows a significant response to salbutamol in asthma patients, but not in those with COPD. Pre- and post-bronchodilator FEV_1/FVC ratios remain almost the same in the COPD group, whereas in comparison the ratio increases significantly in the asthma group post-bronchodilator.

Do patients with asthma and COPD react selectively to different bronchodilators?

Apparently, short-acting anticholinergics are effective bronchodilators when compared with short-acting β_2-agonists in patients suffering from COPD; this behaviour is exactly the opposite of what is observed in patients with asthma.

In the study of Petrie and Palmer [14], salbutamol was significantly more effective than ipratropium bromide in patients with asthma, but in patients with bronchitis there was no significant difference between salbutamol and ipratropium bromide. van Schayck *et al.* [15] studied the bronchodilating responses to 400 µg salbutamol and 80 µg ipratropium bromide in 188 patients with chronic bronchitis or asthma. When patients were categorised into those with a better response to salbutamol and those with a better response to ipratropium bromide, patients with chronic bronchitis responded better in general to ipratropium bromide whereas asthmatic patients responded better to salbutamol. van Schayck *et al.* [15] observed additionally that the response pattern was also related to allergy and age: allergic patients and patients aged <60 years were more likely to respond better to salbutamol 400 µg than nonallergic patients and older patients, who benefited more from ipratropium bromide 80 µg. The response pattern was not related to sex, smoking habits, lung function, bronchial reactivity, respiratory symptoms, or number of exacerbations during the preceding year.

Small, early studies tend to favor the use of anticholinergics in asthma [16]. However a more recent Cochrane review concluded that overall there is no justification for routinely introducing anticholinergics as part of add-on treatment for patients whose asthma is not well controlled on standard therapies [17]. This does not exclude the possibility that there may be a subgroup of patients who derive some benefit and a trial of treatment in individual patients may still be justified. In effect, there appears to be variability in anticholinergic response among asthmatics, probably related to the amount of parasympathetic generating symptoms in various subgroups [18]. The patients most likely to respond to anticholinergic agents are older, intolerant of β_2-agonists or have nocturnal or intrinsic asthma [18]. In any case, Expert Panel Report 3 states that ipratropium bromide may be used as an alternative bronchodilator for patients who do not tolerate short-acting β_2-agonists, although it has not been compared to short-acting β_2-agonists [1].

Many studies have focused on the difference between anticholinergics and β_2-agonists in COPD patients. Braun *et al.* [19] documented that ipratropium produced a better peak response than salbutamol in the majority of subjects. There appeared to be individual differences in responses to both bronchodilators. However, the effect on peak response and duration appeared to be better than that of β_2-agonists in treating those patients with more severe disease and at least equal in treating patients with moderate disease.

In a study of Calverley *et al.* [11] that explored the impact of salbutamol and ipratropium in COPD, both FEV_1 and FVC increased significantly after inhaled salbutamol at the first occasion (V0) (mean change in FEV_1 128±4 mL, mean change

in FVC 286±12 mL). A further significant increase in both variables occurred after ipratropium. Pre-bronchodilator FEV_1 at the next attendance (V1) was lower than at V0, and the increase in FEV_1 after ipratropium (the first drug given at V1) was larger than when salbutamol was given first at V0. The change in FEV_1 when ipratropium was added to salbutamol at V0 was 63±4 mL, and the change when salbutamol was added to ipratropium at V1 was 39±4 mL (difference 24 mL). There were no significant differences in mean post-bronchodilator FEV_1 between V1 and the third visit (V2) or in the mean bronchodilator response at any visit. The intraclass correlation coefficient for pre-bronchodilator FEV_1 was 0.91 and for post-bronchodilator FEV_1 was 0.93 for the three visits.

MAHLER *et al.* [20] explored the differences between a LABA (salmeterol) and ipratropium. They documented that salmeterol was significantly better than ipratropium in improving lung function and health status, and at reducing symptoms at the recommended doses over a 12-week period in patients with COPD. However, data from three studies specifically designed to explore the potential differences between tiotropium and salmeterol seem to indicate greater efficacy for tiotropium, a long-lasting anticholinergic agent (LAMA) [21–23].

Which type of inhaled bronchodilator is most efficacious in the long-term treatment of asthma or COPD?

Over time, LABAs have become a very common treatment in both asthma and COPD, although controversy has reigned over regular LABA use prescribed as monotherapy in the management of asthma [24]. A recent analysis of more than 40,000 asthmatics [25] found that regular LABA use as monotherapy reduced acute exacerbations requiring oral corticosteroids by 20%, and withdrawals due to acute exacerbations by 32%. Additionally, this analysis did not identify any detrimental effect of LABAs on acute exacerbations requiring hospitalisation or on life-threatening episodes. These findings disagree with those by SALPETER *et al.* [26], which supported the concept that regular β_2-agonist use leads to increased airway inflammation and worsening of asthma control. However, factors such as age (children), LABA choice (salmeterol), and duration of treatment (>12 weeks) were associated with an increased risk of serious adverse effects; LABAs as monotherapy were associated with a significant increase in asthma-related deaths, although the size of this increase had a high grade of uncertainty (95% confidence interval ranging from one extra death for every 703–10,585) [25].

Although mild COPD is often treated with "as-required" β_2-agonist, regular high-dose inhaled or nebulised β_2-agonists have been much more widely used in COPD than in asthma. While improvements in lung function and symptoms have been demonstrated in severe COPD, the overall effect on lung function has generally been small [27]. There have been no data suggesting deterioration in lung function following chronic administration of high doses of β_2-agonist in COPD, although there have been concerns about other effects of high doses of β_2-agonist in this setting [28]. In particular, in patients with cardiovascular disease, β_2-agonists should be used cautiously, as they are known to cause hypokalaemia and both supraventricular and ventricular arrhythmias and, consequently, they may exacerbate underlying cardiac disease [29].

Anticholinergics are less useful in asthma than in COPD, as inhaled β_2-agonists are generally more effective [16, 30]. Nonetheless, it has been highlighted that there is considerable variation in responsiveness to an anticholinergic agent among asthmatic patients, with a few responding as well to it as to a β_2-agonist [31]. In particular, older patients and those with intrinsic asthma are most likely to respond favourably to anticholinergic agents [31]. However, clinically useful responses to an anticholinergic agent have been reported in some asthmatic children aged 10–18 years [31]. In general, it has not been possible to predict reliably which asthmatics will obtain benefit from ipratropium other by an individual trial [31]. For those rare asthmatic patients who cannot tolerate the adverse effects that a β_2-agonist may produce, ipratropium may be a useful alternative bronchodilator [31]. Similarly, ipratropium may be useful in treating asthma of psychogenic origin [31].

The major clinical use of inhaled anticholinergic agents is for the routine treatment of stable COPD [31]. A recent meta-analysis suggested that inhaled anticholinergics significantly reduce severe exacerbations and respiratory deaths in patients with COPD, while β_2-agonists are associated with an increased risk of respiratory deaths [32]. This suggests that anticholinergics should be the bronchodilator of choice in patients with COPD, and β_2-agonists may be associated with worsening of disease control. In any case, several studies have now shown that the use of LAMAs is superior in improving health outcomes. Treatment trials in COPD show that greater benefit in symptom

control and lung function is obtained using tiotropium compared with either short-acting anticholinergics (ipratropium) [33], or LABAs [21–23].

Combining bronchodilators with different mechanisms of action

For COPD patients whose condition is not sufficiently controlled by monotherapy, combining bronchodilators of different classes is a convenient way to deliver treatment and obtain improved lung function and other symptoms [3, 4]. A combination of short-acting bronchodilators of differing mechanisms has been used as COPD therapy for many years [34], although a meta-analysis has suggested that the addition of a β_2-agonist to an anticholinergic agent does not improve clinical outcomes (such as reduction in exacerbation frequency) beyond that achieved with an anticholinergic agent alone [33]. Nonetheless, recent clinical trials have shown that the improvement in lung function achieved with a combination of a LABA and a LAMA is greater than treatment with either bronchodilator alone [35–40]. Moreover, a LABA–LAMA combination is more effective than treatment with either bronchodilator alone in reducing the rate of exacerbations [39]. Nonetheless, a longer-duration trial, the Canadian Optimal Management Trial, has shown no clinical advantage of combining tiotropium with salmeterol [41]. Therefore, further long-term studies are required to determine whether the combination of LABA and LAMA has a real clinically relevant effect. In any case, looking at the aforementioned trials, one might argue that it is possible that the type of LABA included in combination with tiotropium can make a difference in the result and that, apparently, the presence of formoterol rather than salmeterol might ensure better outcomes.

Current guidelines for the management of asthma recommend that ipratropium be added when the response to initial treatment with a short-acting β_2-agonist alone is less than complete or poor [2]. In effect, some older studies reported that the combination of ipratropium and fenoterol was effective in stable asthma, offering a stronger bronchodilation and a more prolonged effect than ipratropium or fenoterol alone [42, 43]. No difference was reported when the combination of ipratropium and fenoterol was compared with salbutamol, although the combination contained less β_2-agonist agent [44]. More recently, in a well-defined group of symptomatic, moderate-to-severe asthmatics who were not fully reversible with salbutamol, the fixed combination of ipratropium and salbutamol resulted in a significant increase in FEV_1 area under the curve from 0–6 h post-administration (AUC0–6) response and peak FEV_1 response compared with salbutamol alone after a single-dose administration of each agent [45]. Duration of action was longer with the combination compared with salbutamol alone. These therapeutic findings are important in moderate-to-severe asthmatics who remain symptomatic despite continued use of salbutamol alone for relief.

Recent research has indicated that the addition of salmeterol and tiotropium in association with halving the dose of fluticasone propionate in severe asthmatics leads to small improvements in effort-dependent and -independent pulmonary function outcomes, but not in quality-of-life scores [46]. The magnitude of improvements in pulmonary function provided by salmeterol and tiotropium were not predicted by the acute reversibility to salbutamol and ipratropium.

Inhaled corticosteroids

There is strong evidence that ICS must be used as first-line therapy for the treatment of persistent asthma in adults and children, as they are very effective in reducing symptom severity, improving pulmonary function, reducing bronchial hyperresponsiveness, reducing rescue inhaler use and reducing exacerbations and hospitalisations. Moreover, they may prevent airway remodelling (lung scarring). The clinical improvement in asthma is associated with a significant inhibition of almost every aspect of the inflammatory process. In particular, eosinophilic inflammation is markedly suppressed by corticosteroids, with the disappearance of eosinophils from the airways and sputum [47, 48].

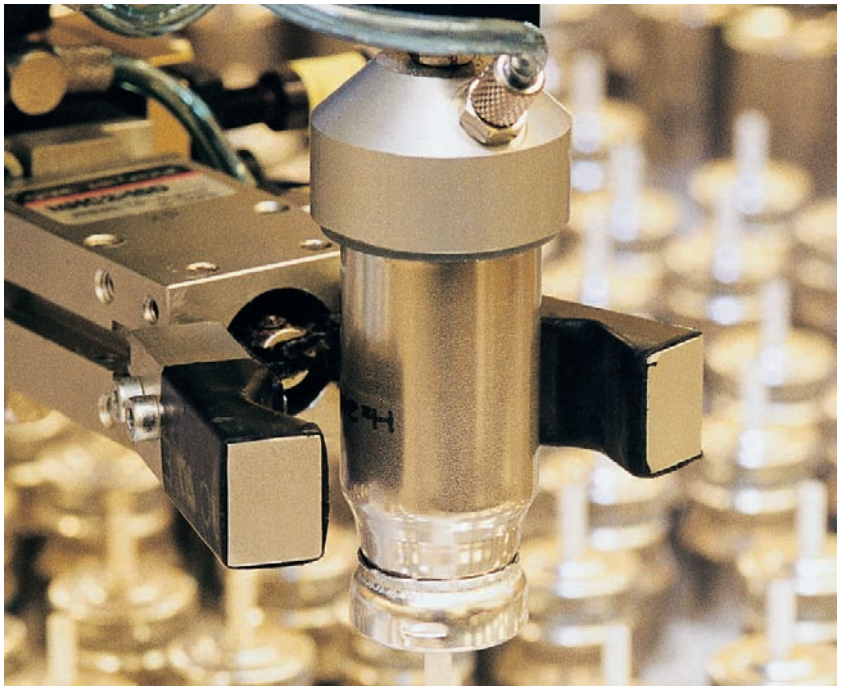
ICS monotherapy achieves successful control of persistent asthma in a significant proportion of patients. Although there is no relationship between ICS dose and FEV_1, there may be a dose-related response with respect to other pertinent outcomes, such as reduction in prednisone dose, bronchial hyperresponsiveness, and cortisol suppression [49]. For the majority of patients, even at low doses, ICSs rapidly improve clinical symptoms and measures of lung function.

Guidelines highlight that early intervention with ICS in newly diagnosed asthma might reduce other aspects of future risk, including the degree of progressive loss of lung function that can occur in asthma and the influence of the overall treatment response [1]. In effect, results from the Inhaled Ster-

oid Treatment As Regular Therapy in Early Asthma (START) study, which assessed whether early intervention with a low dose of the ICS budesonide in patients with <2 years of mild persistent asthma would prevent severe asthma-related events and accelerated decline in lung function, support current guideline recommendations for the daily use of ICS therapy in adults and children with mild persistent asthma [50]. The results from the START study also indicate that early intervention with ICSs improves overall treatment effectiveness and reduces the need for additional medication required to maintain asthma control [50]. AGERTOFT and PEDERSON [51] showed that after 3 years of treatment with ICSs, children who had started this therapy >5 years after the onset of asthma had significantly lower FEV_1 (96% pred) than the children who received ICS within the first 2 years after the onset of their asthma (101% pred) [51]. Intriguingly, it has been reported that regularly scheduled treatment with an ICS for mild persistent asthma has no significant advantage over intermittent short-course treatment [52]. In any case, two observational studies suggest that long-term treatment with an ICS in asthmatic adults is associated with a more favourable decline in FEV_1 with age compared with the natural course of the disease [53, 54]. The use of ICSs on a regular basis also leads to reduced mortality from asthma. Using the Saskatchewan Health data, it has been calculated that the rate of death from asthma decreased by 21% with each additional canister of ICS used in the previous year [55].

In contrast, the place of ICSs in the management of COPD is still controversial despite the fact that active airway and lung inflammation is present. Corticosteroids do not appear to have any effect on the inflammation in COPD, with no changes in neutrophilic inflammation, reduction in inflammatory mediators, or proteases [56].

A pooled analysis of FEV_1 decline in COPD patients randomised to ICS showed that in the first 6 months of treatment, ICS therapy is more effective at improving lung function in ex-smokers than in current smokers with COPD, and females may have a greater response to ICS than males [57]. However, it seems that after 6 months, ICS therapy does not modify the decline in FEV_1. In any case, another pooled analysis based on intention to treat, of individual patient data from seven randomised trials (involving 5,085 patients), published by SIN *et al.* [58], indicates that ICSs are likely to be effective in reducing all-cause mortality in stable COPD. However, the Towards a Revolution in COPD Health (TORCH) study demonstrated that monotherapy with an ICS increased (although in a



nonsignificant manner) the risk of death compared with the placebo group, and there was an excess of patients who received a diagnosis of pneumonia among those receiving study medications containing the ICS [59] . Considering that the rate of FEV_1 descent is an imperfect surrogate outcome for clinically important health outcomes, such as exacerbations, a third meta-analysis, which systematically reviewed the efficacy, effectiveness and safety of ICSs, suggested that COPD patients treated with ICSs experience significantly fewer exacerbations than patients on placebo [60]. The relative risk reduction was 33%; the number needed to treat to prevent one exacerbation during 20.8 months was 12. This treatment effect is apparently stronger in patients with moderate-to-severe COPD. This is an important finding that justifies the use of ICSs in patients with moderate-to-severe COPD, although the COPE study showed that only a minority of patients will develop recurrent exacerbations following ICS withdrawal [61], whereas the COPD and Seretide: a Multi-Center Intervention and Characterization (COSMIC) study showed a doubling of the incidence rate of mild exacerbations, but not moderate-to-severe exacerbations, in the year after withdrawing ICS in COPD patients also using salmeterol [62].

It can be concluded that ICSs have proven to be clinically beneficial in asthma, decreasing exacerbation rates, improving lung function long-term, diminishing decline in lung function, decreasing airway remodelling and reducing the need for use of supplemental medications. In COPD, ICS have been useful in disease phenotypes where patients

Table 5 Inhaled corticosteroids

Asthma	COPD
First-line therapy even in mild persistent disease	Modest effect on long-term deterioration in lung function
Improve lung function and symptoms and health status, decrease exacerbations	Significant decrease in exacerbations
Decrease mortality	Significant improvement in health status
Significant anti-inflammatory effects	No effect on mortality
	Recommended by guidelines for severe disease and in patients with recurrent exacerbations
	Increase risk of pneumonia

with COPD have greater degrees of bronchodilator response, evidence of allergic or inflammatory response, frequent exacerbations or a labile course. Table 5 differentiates responses to ICS in asthma from those observed in COPD and describes the different therapeutic indications.

It should be mentioned that asthmatic patients who smoke have more severe disease and are also resistant to the anti-inflammatory effects of corticosteroids [63]. Smoking asthma patients can be considered as a specific group, intermediate between nonsmoking asthma and COPD patients, with a mixture of the features of both diseases. Plausible explanations for the reduced sensitivity to ICSs in smokers with asthma are noneosinophilic airway inflammation, impaired glucocorticoid receptor function, and/or reduced histone deacetylase activity [64].

Combination therapy with LABA and ICS

There is evidence suggesting that when taken together with ICS, a LABA improves the penetration of ICS into lung cells [63]. Therefore, international and national guidelines highlight that combination therapy with a LABA and an ICS is the preferred treatment when a medium dose of ICS alone fails to achieve control of asthma [1, 2]. Addition of LABAs to a daily regimen of ICSs improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of rapid-acting inhaled β_2-agonists, reduces the number of exacerbations and achieves clinical control of asthma in more patients, more rapidly, and at a lower dose of ICS than ICS given alone. Controlled studies have shown that delivering this therapy in a combination inhaler is at least as effective as giving each drug separately. In any case, a combination ICS–LABA therapy may be considered for patients with poor asthma control whose adherence to ICS inhalers is poor (*i.e.* less than 2 inhalations per day). In fact, use of an ICS–LABA combination inhaler increases adherence to ICS [65]. Patients experience some symptomatic relief taking a LABA, and this is partly supported by patients on ICS–LABA inhalers ordering fewer short-acting β_2-agonist inhalers. A larger study with a higher response rate is needed to confirm this. Better immediate symptom control may reinforce the need to take the combination inhaler, whereas ICS inhalers produce no relief: any beneficial effect takes time to appear, and when inhaler use stops its effects take time to wear off.

Several large-scale studies in patients with moderate-to-severe COPD have demonstrated that ICS–LABA combination treatment leads to significantly greater improvements in lung function, exacerbations, health status and breathlessness, compared with placebo or monotherapy with either of the component drugs [66]. The TORCH findings support the use of combination therapy in patients with moderate-to-severe COPD [59]. The combination of salmeterol and fluticasone clearly reduces the risk of exacerbations and improves health status and lung function. It probably has some positive effect on mortality, though this is modest. Pneumonia risk may also increase with combination therapy. It is important to highlight that because of the results of the TORCH study [59], the salmeterol–fluticasone combination is now indicated for the symptomatic treatment of patients with COPD, FEV_1 <60% pred (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. Prior to the label update, this was only indicated when a patient's lung function had deteriorated to an FEV_1 of <50% pred. However a recent paper published by RABE *et al.* [67] documented that the combination of once-daily tiotropium plus twice-daily formoterol is superior to salmeterol–fluticasone twice-daily in daytime lung function outcomes over 6 weeks in patients at GOLD stages II and III, which is moderate-to-severe COPD.

The clinical evidence thus supports the use of the combination therapy in asthma, in which, however, the LABA must always be considered as an added second controller when it is needed. In contrast, in COPD, there are still doubts about the

Table 6 Combination therapy with long-acting β_2-agonists and inhaled corticosteroids

Asthma	COPD
LABAs as the add-on therapy	ICS as the add-on therapy
Preferred treatment when a medium dose of ICS alone fails to achieve control of asthma	Recommended by guidelines for symptomatic patients with COPD with an FEV_1 < 50% pred (stage III, severe COPD and stage IV, very severe COPD) and repeated exacerbations. However, it is now also indicated for the symptomatic treatment of patients with COPD, FEV_1 <60% pred (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.
Improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of rapid-acting inhaled β_2-agonists, reduces the number of exacerbations	Improves symptom scores, improves lung function but does not influence its long-term deterioration, decreases the use of rapid-acting inhaled β_2-agonists, reduces the number of exacerbations
	Modest effect on mortality
	Increased risk of pneumonia

usefulness of this type of treatment. The real problem that we have when we prescribe a treatment for a patient with COPD is that we tend to treat that patient as a member of a general population with uniform characteristics, since we consider COPD as a homogeneous disease. On the contrary, COPD is a heterogeneous disease that has characteristics that occur in different phenotypes. It is likely that definition of these phenotypes will allow us to understand which kind of patients can benefit from an ICS and which, instead, should only be treated with long-acting bronchodilators. In the meantime, it must be mentioned that the use of ICS–LABA combination therapy has been shown to be effective in both asthma and in many patients suffering from COPD, perhaps suggesting that there are some similar pathophysiological characteristics in these two diseases.

Table 6 differentiates responses to ICS–LABA combination therapy that are observed in asthma from those observed in COPD and describes the different therapeutic indications.

Conclusion

It is now clear that the aims of treatment in asthma are to decrease inflammation and to obtain total control. In COPD, the aims of treatment are different: it is important to prevent the development of the disease, but it is not an easy job. Therefore, we must mainly try to reduce symptoms and to prevent exacerbations that influence the progression of the disease.

When we are treating an asthmatic patient, we can influence eosinophilic inflammation (CD4 type), bronchoconstriction and mucus production, whereas when we are treating a COPD patient, we can try to influence neutrophilic inflammation (CD8 type), and again, bronchocostrition and mucus production. However, with the present therapy, we can not modify small-airway remodelling in asthma and small-airway remodelling, loss of alveolar attachments and collagen/elastin destruction in COPD (table 7).

In any case, (early) treatment can influence some outcomes in asthma and COPD (table 5). It can influence morbidity and mortality, quality of

Table 7 What we can or cannot modify with therapy in asthma and COPD

Asthma	COPD
What we can modify	
Morbidity/mortality	Morbidity/mortality
Quality of life	Quality of life
Cost	Cost
Natural history (??)	Natural history (only with smoking cessation)
What we cannot modify	
Small-airway remodelling	Small-airway remodelling
	Loss of alveolar attachments
	Collagen/elastin destruction

Further reading (guidelines)

ATS/ERS Standards for diagnosis and treatment of COPD. *Eur Respir J* 2004; 23: 932–946
www.ers-education.org/pages/default.aspx?id=725

British Thoracic society/SIGN guidelines on asthma 2008 (revised 2009).
www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Asthma/Guidelines/Asthma_fullguideline_2009.pdf

life and costs in both diseases. We still do not know whether a regular treatment can influence the natural history of asthma, whereas we know that only smoking cessation is able to do it in COPD.

The present reality is that asthma and COPD are not yet curable, they are underdiagnosed and undertreated, and therapy is still evolving. The good news is that there is now a better understanding of pathology of these two diseases and new lines of promising drugs, and mainly that we have understood that proper management means a normal or almost-normal life.

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