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# Emerging trends in the therapy of COPD: bronchodilators as mono- and combination therapies

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**Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease that is characterized by progressive airway obstruction that, unlike asthma, is relatively insensitive to bronchodilators and to the classic anti-inflammatory therapy, corticosteroids. In this review we consider the potential of bronchodilator drugs and corticosteroid drugs that are in clinical development for COPD and discuss how the best treatments might be achieved with combinations of drugs that are either already launched or close to launch.**

## Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide with an overall prevalence in adults aged >40 years estimated currently at 9–10% [1]. The World Health Organization (WHO) estimates that, by 2020, COPD will be the third leading cause of mortality and the fifth leading cause of morbidity in the world. The primary cause of COPD is smoking, with 30–40% of smokers estimated to develop the disease [2].

COPD is characterized by airflow obstruction that deteriorates progressively and has a limited reversibility following bronchodilator therapy. The decline in lung function in healthy individuals is ~30 ml year$^{-1}$ whereas the decline in moderate to severe COPD patients is ~60 ml year$^{-1}$ [3]. COPD patients present with cough, sputum production and breathlessness, and suffer frequent exacerbations of the disease that can be bacterial, viral or idiopathic in nature [4]. Notably, patients with frequent exacerbations have a reduced quality of life and a more rapid decline in lung function [5]. Disease severity (Stage 0 to Stage IV) is classified according to the extent of airflow limitation during forced expiration and is based specifically on the post-bronchodilator forced expiratory volume in one second ($FEV_1$). This disease classification is provided by the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines [6]. The clinical features of COPD are summarized in Table 1.

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## Aims of therapy

The aim of therapy for COPD is to prevent and control symptoms and reduce mortality by reducing the frequency and severity of exacerbations, improving health status and exercise tolerance, and, ultimately, preventing the accelerated decline in lung function. Reducing the frequency and severity of exacerbations is an increasingly important therapeutic target because the prognosis for patients following exacerbations is considered to be poor. An investigation into patient survival following hospital admission for acute exacerbations reveals an 11% in-hospital mortality rate, and high 1- and 2-year mortality rates (43% and 49%, respectively) [7]. A recent retrospective analysis, which examined survival up to 5 years post-hospitalization, demonstrates a mortality rate of 69.6% with a median survival rate of 26 months [8].

## Current therapy for COPD

### *Bronchodilators ($\beta_2$ adrenoceptor agonists and muscarinic $M_3$ receptor antagonists)*

Although the airway obstruction in COPD was considered originally as fixed and irreversible there is significant evidence that a component of this is partially reversible and responsive to bronchodilators [9,10]. Current therapy, thus, focuses on the early use of bronchodilators, which can be categorized as either short acting (~4 h duration) or long acting (>12 h duration). Currently, two main types of bronchodilators are in clinical use: $\beta_2$ adrenoceptor agonists (stimulation of the receptor increases cAMP concentration, resulting in airway smooth-muscle relaxation) and muscarinic ($M_3$) acetycholine (ACh) receptor antagonists,



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**TABLE 1**

**Clinical features of COPD**

| | Key characteristics associated with COPD | Refs |
|---|---|---|
| Risk factors | Continued smoking<br>Age<br>Air pollution<br>Genetic | [51,52] |
| Airflow obstruction | Progressive decline (60 ml year$^{-1}$ compared to 30 ml year$^{-1}$ in normal subjects)<br>Limited reversibility with bronchodilators | [3,9,10] |
| Symptoms | Cough<br>Sputum production<br>Breathlessness | [53] |
| Exacerbations | Frequent: associated with reduced quality of life and a more rapid decline in lung function<br>Bacterial, viral or idiopathic | [4,5] |
| Severity classification | Based on post bronchodilator forced expiratory volume in one second ($FEV_1$) (GOLD Stages 0 to IV) | [6] |

which antagonize the constricting effect of ACh on airway smooth muscle. Both types of bronchodilator provide effective symptomatic relief and are currently the first-line therapy of choice for the treatment of airway constriction [6]. Key to understanding the therapeutic value of bronchodilators in a disease that is relatively insensitive to bronchodilators is their effects on dynamic hyperinflation of the lungs of COPD patients. Dynamic hyperinflation results when air is trapped within the lungs after each breath because of a difference in the volume of air that is moved during inhalation and expiration. Full expiration depends on the degree of airflow limitation and the time available for exhalation. Both these parameters vary, causing greater hyperinflation during periods associated with either exacerbations or exercise [11]. In COPD, bronchodilators reduce dynamic hyperinflation during exercise by increasing the diameter of the airways, which reduces expiratory airflow resistance and results in an increase in expiratory flow [12].

A review of the use of long-acting bronchodilators has compared the effects of once-daily treatment with the muscarinic receptor antagonist tiotropium, and twice-daily treatment with the $\beta_2$ adrenoceptor agonists formoterol and salmeterol on key outcome measures, including lung function, symptomatic relief and reduction in exacerbation frequency [13]. This critical review reported that all three long-acting bronchodilators improve lung function effectively; however, they differ in their effects on outcomes other than lung function, with salmeterol having inconsistent efficacy compared with placebo in preventing exacerbations and improving health status, and only tiotropium showing consistent superiority to the short-acting bronchodilator ipratropium. Although formoterol performed more consistently than salmeterol, possibly because it is a full agonist at $\beta_2$ adrenoceptors, it is less effective than tiotropium. Additional data from retrospective analysis of a 1-year, placebo-controlled clinical trial, indicates that tiotropium is associated with a reduced rate of decline in lung function after 1 year (59 ml year$^{-1}$ in the placebo group and 19 ml year$^{-1}$ in the tiotropium group) [3]. The UPLIFT trial (Understanding Potential Long-term Impacts on Function with Tiotropium), the results of which are due in 2008, has been designed specifically to confirm this observation. A systematic review of the efficacy of tiotropium in COPD has been published recently [14], and indicates that this drug has a positive impact on reducing exacerbations of COPD and related hospitalizations, and improves quality of life.

A recent meta-analysis of >15000 patients highlights the potential advantage of muscarinic receptor antagonists (tiotropium and ipratropium) over several $\beta_2$ adrenoceptor agonists including formoterol, salmeterol and albuterol in the treatment of COPD. This analysis reveals that muscarinic receptor antagonists reduce severe respiratory events by 33% and respiratory-related deaths by 7%, compared with placebo. Effects on mortality have not been the primary outcome of clinical trials of muscarinic receptor antagonists for the treatment of COPD, so the findings of this meta-analysis need to be confirmed in appropriately designed trials before drawing firm conclusions. The same meta-analysis found that regular inhalation of $\beta_2$ adrenoceptor agonists increases the risk of respiratory death by over two-fold compared with a placebo, and increases the risk of severe exacerbations two-fold compared to muscarinic receptor antagonists [15]. In asthma studies, monotherapy with long-acting $\beta_2$ adrenoceptor agonists (LABAs) has been suggested to slightly increase the risk of death from asthma compared with short-acting $\beta_2$ adrenoceptor agonists in a small but significant subpopulation of patients [16]. This has resulted in a 'black box' warning on the prescription label [17]. Currently however, it is unclear if this is also the case for COPD patients.

### *Inhaled corticosteroids: $\beta_2$ adrenoceptor agonist combinations*

The efficacy of inhaled corticosteroids (ICS) as a monotherapy in COPD has been evaluated in three long-term trials [18], none of which demonstrate an improvement in lung-function decline, and meta-analysis of six studies of >2-year duration in 3571 patients supports the view that ICS do not improve the decline in lung function [19]. These and other data have resulted in failure of the regulatory authorities in the USA and UK to approve ICS as monotherapies for COPD although these products have been approved for asthma for nearly a decade. However, retrospective analyses indicate a potential reduction in all-cause mortality [20] and exacerbation rates [21] although the validity of the statistical methodology employed to determine the effects of ICS on exacerbation rates is under debate [22].

ICS are used increasingly in combination with LABAs, for example fluticasone plus salmeterol (Advair/Seretide) and budesonide

plus formoterol (Symbicort). Three, 1-year, randomized clinical trials have studied the effects of combining a LABA with ICS [23]. In these three studies, overall exacerbation frequency is lower with therapy than placebo. Combination therapy has a similar effect to its individual components in the trial of inhaled steroids and LABAs using salmeterol and fluticasone [24]. However, when patients with more severe COPD ($FEV_1$ <36% predicted value) were studied using a combination of budesonide and formoterol, the overall exacerbation rate improves compared with $\beta_2$ adrenoceptor agonist alone [25,26]. The results of the three-year Towards a Revolution in COPD Health (TORCH) trial to compare the combination of salmeterol and fluticasone with each of its components have been published recently [27]. These data offer convincing evidence that long-term therapy with fluticasone and salmeterol combination reduces exacerbations (25%) and improves health status and lung function. However, the trial does not demonstrate a statistically significant effect of the combination on all cause mortality (17.5% reduction; $P = 0.052$) compared to placebo. These findings support the use of combination therapy with ICS and LABAs in patients with more severe COPD, and will reduce the probability that ICS will be used as monotherapies in COPD. The GSK combination product Advair (in the US) and Seretide (in the EU), was approved for use as a therapy for COPD in 2003. The AZ combination product, Symbicort, was approved for COPD in the EU in 2000 and an NDA (New Drug Application) for COPD is expected in 2008.

ICS alone and in combination with $\beta_2$ adrenoceptor agonists have been investigated extensively for anti-inflammatory activity in COPD patients. The data available are variable and whether ICS are effective as anti-inflammatory agents in COPD remains contentious. A meta-analysis of six studies indicates that ICS monotherapy has some anti-inflammatory activity (reduction in sputum neutrophils), particularly when patients receive higher doses of ICS for >six weeks [28]. By contrast, ICS effectively reduce sputum eosinophils after treatment for two weeks in asthma patients [29]. A recent study using the combination of inhaled fluticasone and salmeterol [30] for 13 weeks demonstrates significantly greater anti-inflammatory activity than with fluticasone alone [31]. The combination of ICS and $\beta_2$ adrenoceptor agonists significantly reduced the absolute numbers of biopsy (CD45+) leukocytes, CD8+ and CD4+ T cells, and decreased the number of cells that express genes encoding the pro-inflammatory mediators interferon $\gamma$ and tumour necrosis factor $\alpha$ but did not inhibit numbers of CD68+ cells (monocyte/macrophages). After 13 weeks, a small reduction in percentage but not in total sputum neutrophils was seen. The relationship between these anti-inflammatory effects and the clinical outcomes (173 ml improvement in pre-bronchodilator $FEV_1$) remains to be established. Further trials that explore whether this combination therapy has a synergistic anti-inflammatory effect in the lungs and systemically are ongoing (http://www.clinicaltrials.gov/ct/show/NCT00116402 and http://www.clinicaltrials.gov/ct/show/NCT00120978).

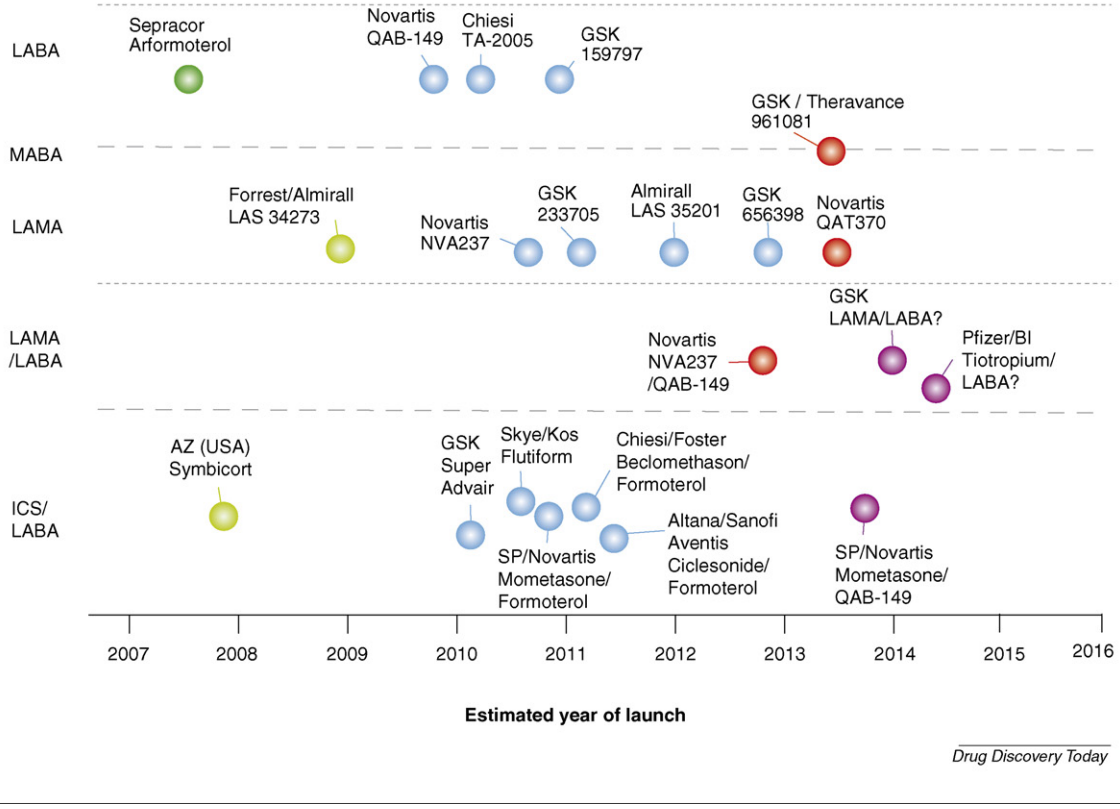


**FIGURE 1**

**Outline of the current status of drugs in clinical development for COPD (bronchodilators and combination products).** Status: launch (dark-green circles); phase III (light-green circles); pahse II (blue circles); phase I (red circles) and pre-clinical (purple circles). Abbreviations: long-acting $\beta_2$ agonist (LABA); long-acting $M_3$ antagonist (LAMA); M3 antagonist-$\beta_2$ agonist (MABA).

## Emerging trends in COPD therapy

Investigational drugs that are currently in clinical development for COPD target several therapeutic strategies and include new, once-daily bronchodilator drugs and novel ICS with long duration of action and a reduced side-effect profile. Based on the success of these approaches, the development of novel dual- and triple-inhalation combinations are anticipated. An outline of the current status of drugs in clinical development for COPD with estimates for year of launch are shown in Figure 1 and described below.

### *New bronchodilator approaches*

*Long-acting $M_3$ receptor antagonists* The efficacy of tiotropium in patients with COPD has played a role in the renewed interest in the potential of bronchodilators, particularly of $M_3$ receptor antagonists. The effect of tiotropium on the frequency and severity of exacerbations is of particular note. In a recent study tiotropium reduces significantly (by 17%) the proportion of patients that experience more than one exacerbation and decreases the number of exacerbations by 35% and exacerbation days by 37% versus placebo [32]. The accumulating positive data has led to an explosion of activity in this area and currently there are six $M_3$ antagonists in clinical development with >40 patents published in the past 18 months (Table 2).

The target for the long-acting $M_3$ receptor antagonists (LAMAs) currently in clinical development is 24-h duration of action coupled with a fast onset of action and a reduced side-effect profile compared to tiotropium. Sosei-Vectura recently licensed their LAMA NVA237 to Novartis and the companies have released promising data that supports a long duration of action and a minimal side-effect profile at the American Thoracic Society (ATS) Meeting [33–36]. The possibility that a selective oral $M_3$ receptor antagonist might have a therapeutic advantage over inhaled compounds has been evaluated in COPD patients without success [37], which indicates that improved $M_3$ receptor antagonists will only be achieved by targeting the inhaled route of delivery.

*LABAs* Currently marketed LABAs are administered twice daily, but several, once-daily LABAs are in clinical development with the primary aim of improving compliance (Table 3). It is anticipated that these will be used either as monotherapies for either asthma or COPD or in combination with either long-acting ICS (Table 4) or LAMAs. Both Sepracor and Novartis presented updates on the clinical progress of their compounds at the ATS meeting in May 2006. In COPD patients, indacaterol is well tolerated, with a rapid onset, sustained duration of action (24 h) and an overall efficacy after 1–8 days administration that is equivalent to Tiotropium [38]. In a dose-ranging study, single doses of arformoterol are either equivalent to or better than salmeterol [39]; this is also the case in a Phase III trial of 12 weeks in which arformoterol caused a significant, sustained improvement in airway function [40]. Sepracor have submitted an NDA for arformoterol for the treatment of COPD to the FDA in February 2006, which was approved as a twice daily therapy for COPD in October 2006. GSK appear to have six $\beta_2$ adrenoceptor agonists in clinical development with the strategy of selecting the optimal, once-daily combination product with a novel corticosteroid (Super Advair) to replace the twice daily salmeterol/fluticasone combination (Advair).

*New combinations of ICS and $\beta_2$ adrenoceptor agonists* The success of Advair/Seretide in COPD (sales of $3.4 billion in the US in 2005) has led increased efforts to launch novel combinations of ICS and $\beta_2$ adrenoceptor agonist. The most advanced of these is Super Advair, which is expected to be launched in the first half of 2010. A key feature of this combination will be once-daily administration. To achieve this goal, GSK and their partner Theravance have two

**TABLE 2**

**$M_3$ receptor antagonists in clinical development**

| Compound ID | Company | Clinical phase | Comment |
|---|---|---|---|
| LAS34273 | Forrest/Almirall | Phase III | Recent licensing deal |
| NVA237 | Novartis/Sosei-Vectura | Phase II | Recent licensing deal<br>Data released at ATS2006 |
| GSK656398 | GSK | Phase II | Joint venture with Theravance |
| GSK233705 | GSK | Phase II | |
| LAS35201 | Almirall | Phase II | |
| QAT370 | Novartis | Phase I | |

**TABLE 3**

**$\beta_2$ adrenoceptor agonists in clinical development**

| Compound ID | Company | Clinical phase | Comment |
|---|---|---|---|
| Arformoterol | Sepracor | Registered | Single isomer of racemic formoterol (nebulizer) |
| Indacaterol | Novartis | Phase II | Combination with NVD237 in preclinical phase |
| Carmoterol | Chiesi | Phase II | Licensed from Tanabe in 2002 |
| GSK159797, GSK59790, GSK159802, GSK642444, GSK678007, GSK96108 | GSK | Phase II | In combination with a corticosteroid (GSK685698 and GSK799943) as part of 'Super Advair' strategy |

**TABLE 4**

**ICS/LABA combinations in clinical development for asthma and COPD**

| Combination | Company | Clinical phase | Comment |
|---|---|---|---|
| Symbicort (budesonide/formoterol) | AZ | Launched in EU<br>Phase III in US | Twice daily |
| Super Advair | GSK | Phase II | Six LABA options in Phase II<br>Two corticosteroids<br>Once daily (see Table 3) |
| Beclomethasone/formoterol | Chiesi/Foster | Phase II | Twice daily |
| Ciclesonide/formoterol | Altana/Sanofi Aventis | Phase II | Twice daily<br>Alternative name: Alvesco Combo |
| Fluticasone/formoterol | SkyePharma/Kos | Phase III | Twice daily<br>Alternative name: Flutiform |
| Mometasone/formoterol | Schering Plough/Novartis | Phase II | Twice daily |
| Mometasone/undacaterol (QAB149) | Schering Plough/Novartis | Preclinical | Once daily |

corticosteroids and up to six $\beta_2$ adrenoceptor agonists in clinical development. Other combinations of ICS and $\beta_2$ adrenoceptor agonists in development include fluticasone/formoterol (Fluti-Form) from SkyePharma/Kos Pharmaceuticals and mometasone/formoterol from Schering-Plough/Novartis, which are estimated to be launched in mid-2010 and late-2010, respectively. In addition, Altana and Sanofi-Aventis have a potential ICS/$\beta_2$ adrenoceptor–agonist combination product, Alvesco Combo (ciclesonide formoterol), which is expected to be launched in the first half of 2011. Potentially, this product offers important safety advantages over existing corticosteroid treatments, especially in patients requiring high-dose ICS [41]. These combination products, unlike Super Advair will be administered twice daily. Schering-Plough and Novartis have announced recently that they will develop a once-daily combination product of mometasone and indacaterol.

Despite the lack of approval for ICS for COPD, new ICS are in clinical development either as part of a once-daily combination product with $\beta_2$ adrenoceptor agonists or as ICS with a unique profile. Topigen have a novel, inhaled, nitric oxide (NO)-donating derivative of budesonide, TPI1020, in Phase II trials. In a guinea-pig model of airway hyperactivity to histamine following LPS challenge the addition of a NO-donating group to budesonide improves the anti-inflammatory profile compared to budesonide alone [42]. Novartis are reported to have a novel corticosteroid, QAE397, in Phase I development for asthma and COPD, although in January 2006 this compound was listed as in development for asthma only.

### *New combination approaches*

The potential for novel inhaled combinations for the treatment of COPD will increase as our understanding of the efficacy of single agents alone increases. New combination products will provide both improved patient compliance and simplified disease management.

### *Combinations of $\beta_2$ adrenoceptor agonists and $M_3$ receptor antagonists*

The area of most intense activity for combination approaches is to combine bronchodilator agents with different mechanisms of action: $\beta_2$ adrenoceptor agonist and $M_3$ receptor antagonist.

A combination of short-acting bronchodilators of differing mechanisms has been used as a therapy for COPD for >10 years. The combination of ipratropium and albuterol, when given by metered-dose inhaler to patients with COPD, is more effective than either of the two agents alone [43]. This might reflect both simple additive effects and/or a true synergy based on a pharmacological interaction that depends on their respective modes of action ($M_3$ receptor antagonism and $\beta_2$ adrenoceptor agonism).

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 [44–47]. However, the authors of a recent meta-analysis [15] suggest that the addition of a $\beta_2$ adrenoceptor agonist to a muscarinic receptor antagonist does not improve clinical outcomes (such as reduction in exacerbation frequency) beyond that achieved with a muscarinic receptor antagonist alone. It is of note that the data in this analysis is from four combination studies using only short-acting bronchodilators. Further trials are required to examine the clinical benefit of LABA/LAMA combinations.

The current clinical strategy for developing a combination product is to administer a once-daily $\beta_2$ adrenoceptor agonist and $M_3$ receptor antagonist in the same inhaler. Novartis, GSK, Boehringer Ingelheim and Pfizer appear to be following this strategy although no combination product is in clinical development. However, GSK (in collaboration with Theravance) are also adopting a different approach and have a dimer molecule in which both pharmacologies are present (these molecules are known as a MABA bronchodilator), and a clinical candidate featuring this property is currently in Phase I trials. Either approach might result in the development of optimum bronchodilator therapy with rapid onset, 24 h duration of action and maximum effects on dynamic hyperinflation. This is anticipated to be an area of considerable focus over the next 2–3 years as companies vie to produce products that deliver two distinct pharmacological actions simultaneously. Such an approach would significantly increase in the number of combination options available and allow the development of the most effective therapy for COPD patients.

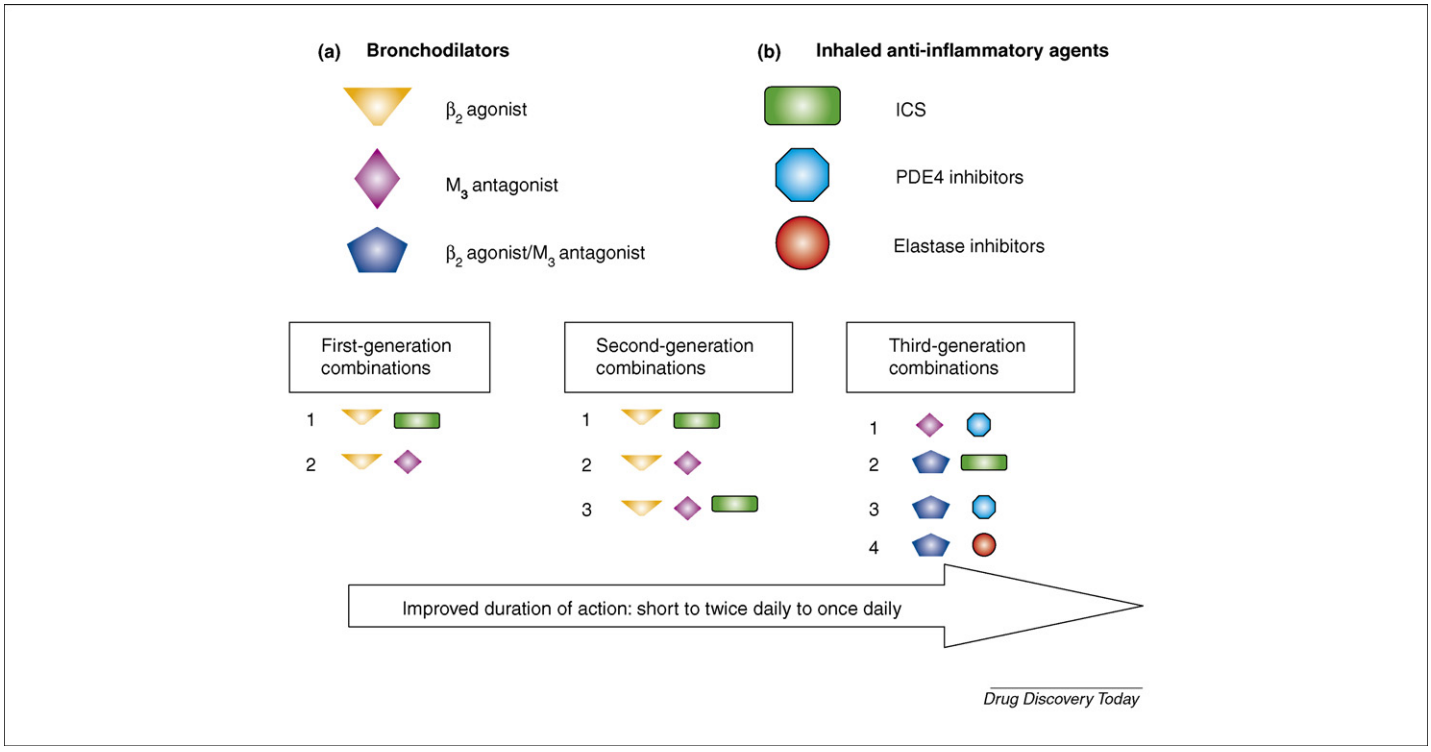


**FIGURE 2**

**Novel inhaled combinations for the treatment of COPD. (a)** Bronchodilators. **(b)** Inhaled anti-inflammatory agents. The numbers refer to different combination options.

### *Combinations of ICS, $\beta_2$ adrenoceptor agonists and $M_3$ receptor antagonists*

The potential for triple combinations is also under discussion, based on the promising data reported for trials with a combination of ICS, $\beta_2$ adrenoceptor agonist and $M_3$ receptor antagonist. The advantage of this combination approach has been studied in two published trials. In addition, a recent patent claims the use of triple combinations for the treatment of obstructive airway diseases [48]. Recently a paper comparing the relative efficacy (symptoms and lung function) of the combination of fluticasone proprionate, salmeterol and tiotropium in patients with severe to very severe COPD has been published [49]. In a 3-month period, administration of the triple combination provided greater improvements in trough $FEV_1$ compared to therapy with fluticasone plus salmeterol or tiotropium given alone. However, this is not accompanied by better symptom control and/or reduced use of rescue medication, so longer-term trials are required to confirm the outcome of this short-term trial in a small number of patients. The Canadian Optimal Management Trial has compared the use of tiotropium in combination with placebo, salmeterol or fluticasone/salmeterol for 12 months in patients with moderate to severe COPD [50]. The results of this trial show that the triple combination compared to tiotropium plus placebo improves lung function, quality of life and hospitalization rates without further reducing exacerbation frequency. By contrast, there is no clinical advantage of combining tiotropium with salmeterol although other shorter-duration trials have indicated a benefit of this combination on lung function. Further long-term studies are required to support these findings and determine whether the triple combination has a clinically relevant effect on rates of exacerbation.

### *Combinations of inhaled bronchodilators and anti-inflammatorys*

The requirement for bronchodilators as a maintenance therapy in COPD will drive the inclusion of improved bronchodilator molecules in any new combination therapy. Combinations of this type will both improve patient compliance and simplify disease management for these patients. The availability of inhalers with two chambers will increase the feasibility of such combinations. The clinical development of the GSK/Theravance MABA will increase the scope of potential combination therapies. Other inhaled anti-inflammatory approaches such as inhibitors of phosphodiesterase 4 (PDE4) are considered to be potential candidates for combination approaches (Figure 2). It is anticipated that the first of these combinations will feature the inhaled PDE4 inhibitor from Pfizer, tofimilast (Phase II) with a LAMA (potentially tiotropium) and then, potentially, with a MABA.

## Conclusions and future perspectives

The area of inhaled combinations is exciting and potentially offers patients the best therapy options for this difficult disease. Although a myriad of combination opportunities can be postulated, those that are most likely to succeed in the near future are based on either currently available single drugs or dual-combination products for which clinical proof of concept is established already (Figure 2). Currently, the main focus is to provide once-daily combination products that should both simplify disease management for patients and improve compliance. The known benefit of ICS/LABA combinations makes these approaches for once- and twice-daily products the most advanced clinically, but

they are being followed rapidly by the new concept of LABA/LAMA bronchodilator combination products. The advent of a successful MABA product will revolutionize the field and open the door for a new range of combination products.

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