# NEWEST PHARMACOLOGIC AGENTS FOR MANAGEMENT OF COPD

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# Newest Pharmacologic Agents for Management of COPD

**ANCC Accredited NCPD Hours: 2 hrs**

**Target Audience: RN/APRN**

## Need Assessment

Chronic Obstructive Pulmonary Disease (COPD) is characterized by a chronic and persistent airflow limitation that is progressive and interferes with normal breathing. It is one of the leading yet under-recognized causes of morbidity and mortality worldwide. Even in people with mild or moderate chronic obstructive pulmonary disease, work productivity is lower than in people without chronic obstructive pulmonary disease and about 3-fold decrease in productivity has been reported in chronic obstructive pulmonary disease patients with symptom burden.

## Objectives

- Discuss the role of inflammation in the pathogenesis of chronic obstructive pulmonary disease
- Describe the role of long acting bronchodilators in management of chronic obstructive pulmonary disease
- Understand how combination bronchodilator works in management of chronic obstructive pulmonary disease
- Identify two combination pharmacologic agents in chronic obstructive pulmonary disease management
- Describe pharmacologic therapy to prevent chronic obstructive pulmonary disease exacerbations

## Goal

The goal of this article is to focus on identifying and managing patients with chronic obstructive pulmonary disease pharmacologically according to their risk and type of exacerbation and discuss current and evolving pharmacologic strategies

# Introduction

Chronic obstructive pulmonary disease is a progressive, irreversible inflammatory disease of the lungs that makes it hard to breathe. Chronic obstructive pulmonary disease (COPD) is associated with high morbidity and mortality. It's a group of lung diseases that block airflow and make it difficult to breathe. Emphysema and chronic bronchitis are the most common conditions that make up chronic obstructive pulmonary disease (as shown in figure 1). Emphysema slowly destroys air sacs in your lungs, which interferes with outward air flow. Bronchitis causes inflammation and narrowing of the bronchial tube, which allows mucus to build up. Chronic obstructive pulmonary disease is typified by persistent, progressive airflow limitation and a range of respiratory and systemic symptoms such as breathlessness, coughing, wheezing, depression, anxiety, general fatigue, and sleeping difficulties (as shown in figure 2). Despite receiving treatment for chronic obstructive pulmonary disease, many patients suffer from regular symptoms that affect their daily lives and lead to increased morbidity. These symptoms vary in severity, frequency and type and can occur at any time throughout the 24-h day, with over half of

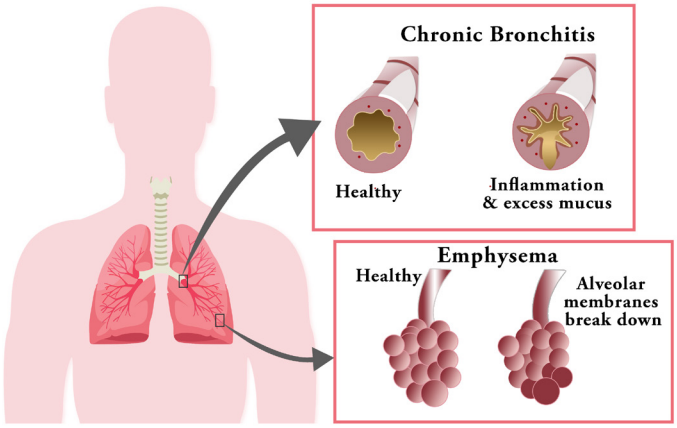


Figure 1: Conditions that make up COPD

patients with chronic obstructive pulmonary disease experiencing symptoms in the morning, during the day and at night-time.

Despite the prevalence of symptoms, patient and physician perception of the impact of chronic obstructive pulmonary disease symptoms on patients' lives is not always in concordance. Dual bronchodilator therapy with a long-acting muscarinic antagonist (LAMA) and long-acting beta agonist (LABA) has the potential to treat the symptoms of chronic obstructive pulmonary disease in addition to improving lung function. The symptoms of chronic obstructive pulmonary disease are troublesome, variable, can occur during all parts of the 24-h day and have a substantial impact on patients' health status and quality of life. In order to provide effective, patient-orientated care, patients with chronic obstructive pulmonary disease should be evaluated on the basis of lung function, the frequency of symptoms, and patient-perceived impact

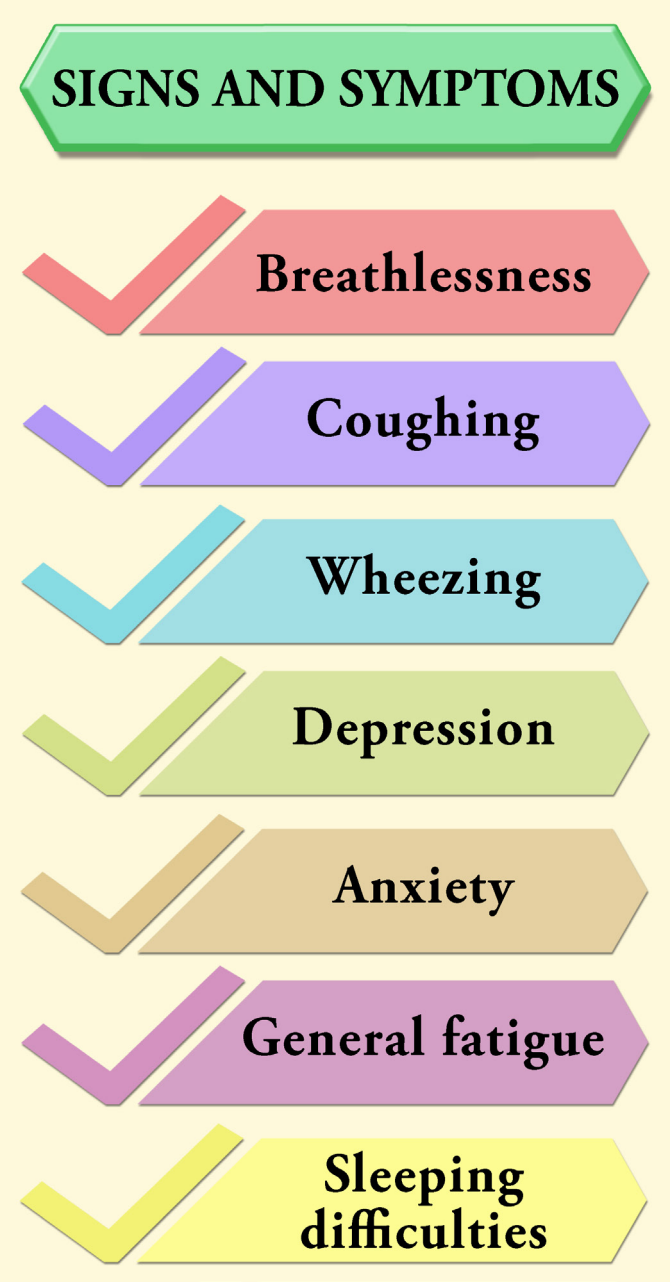


Figure 2: Signs and symptoms of COPD

of symptoms on their lives. Therapy should be chosen carefully based on individualized assessment, ensuring personalization to the individual needs of the patient. [1, Rank 5]

## Overview of Inflammation in the Pathogenesis of chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease results from the combined processes of peripheral airway inflammation and narrowing of the airways. This leads to airflow limitation and the destruction and loss of alveoli, terminal bronchioles and surrounding capillary vessels and tissues, which adds to airflow limitation and leads to decreased gas transfer capacity (as shown in figure 3). The cellular inflammation in stable chronic obstructive pulmonary disease is characterized by the presence of increased numbers of macrophages, neutrophils, T lymphocytes, dendritic cells and B lymphocytes. Increased numbers of neutrophils and B lymphocytes are usually associated with the most severe chronic obstructive pulmonary disease. During chronic obstructive pulmonary disease exacerbations, there is also a recruitment of eosinophils, particularly during virus-induced severe chronic obstructive pulmonary disease exacerbations. T lymphocytes in chronic obstructive pulmonary disease are predominantly CD8+, but CD4+ cells are also increased. T-helper (Th)-1 and T-cytotoxic (Tc)-1 subtypes, characterized by production of interferon (IFN)-γ, predominate, although

"Chronic obstructive pulmonary disease is an umbrella term for a group of conditions involving progressive and irreversible lung damage.

Symptoms are often referred to as "smokers cough" or a natural part of ageing rather than an incurable disease."

Th2 cytokines are also increased in stable chronic obstructive disease patients with increased interleukin (IL)-4 expression in CD8+ cells (Tc2 cells) from bronchoalveolar lavage (BAL).

In the blood there are increased proportions of IFNγ+ and TNFα+ , CD8+ T-cells in stable chronic obstructive pulmonary disease patients correlating with Global initiative for chronic obstructive lung disease grades when compared with healthy never-smoking controls. An increased number of Th17 cells are also present in bronchial biopsies of patients with stable chronic obstructive pulmonary disease.

"T lymphocytes in chronic obstructive pulmonary disease are predominantly CD8+"

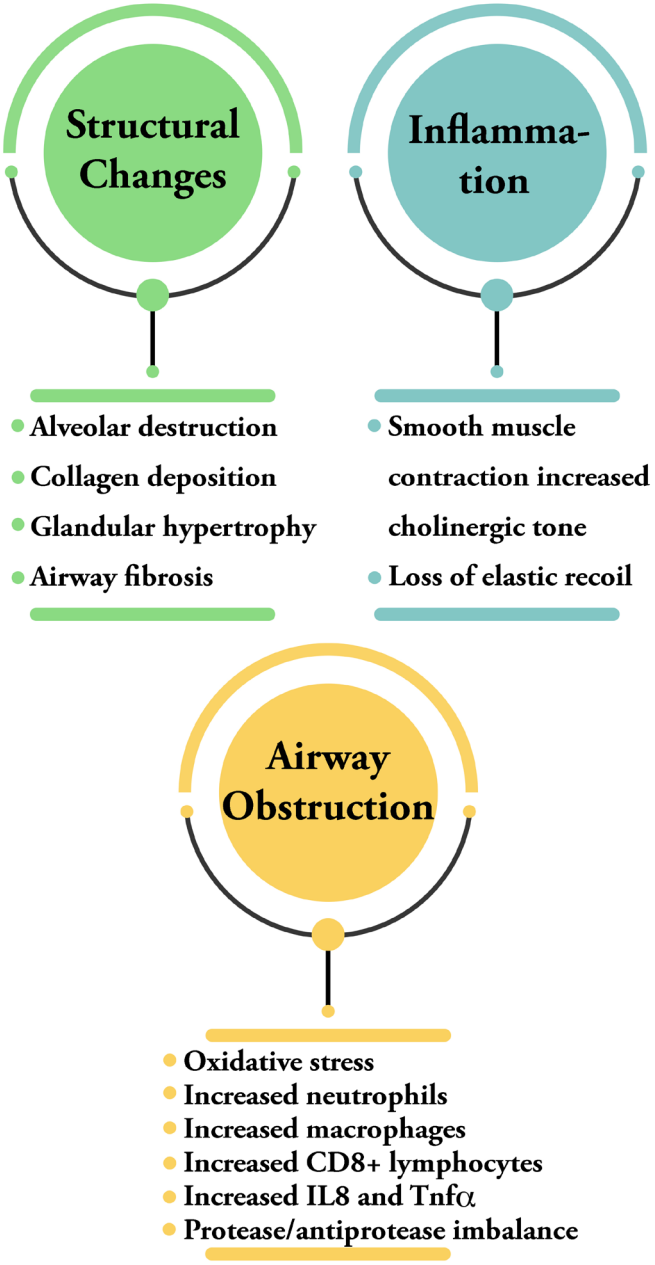


Figure 3: Pathogenesis of COPD

Many inflammatory cells and mediators are involved in the inflammatory process of chronic obstructive pulmonary disease (as shown in figure 4). It is clear that cigarette smoke itself can directly activate many cells, such as epithelial cells or macrophages, to release cytokines and chemokines, leading to inflammatory cell recruitment and activation and to tissue

destruction. TNFα, IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), and CXCL8 (IL-8) are released by airway epithelial cells exposed to cigarette smoke, in addition to transforming growth factor (TGF)-β1, which is implicated in the activation of myofibroblasts and airway smooth-muscle cells to cause proliferation and fibrosis. Alveolar macrophages are also activated by cigarette smoke extract to release a similar profile of cytokines as epithelial cells, including TNFα, CXCL8, CCL2 (monocyte chemo attractant protein [MCP]-1) in addition to leukotriene B4 and oxidants (reactive oxygen species). Alveolar macrophages, like bronchial epithelial cells, can also release a number of other chemokines, including CXCL9 (monokine-induced by IFNγ), CXCL10 (IFN-inducible protein 10) and CXCL11 (IFN-inducible T-cell alpha chemo attractant), which are chemotactic for CD8 T cells through the CXCR3 receptors. In addition, there is the synthesis of elastolytic enzymes, such as matrix metalloproteinase-2 (MMP-2), MMP-9, MMP-12 and cathepsins. Regulation of these cytokines is likely to be under the control of nuclear factor (NF)-κB, which is activated in macrophages from chronic obstructive pulmonary disease patients. An increased number of macrophages in the lungs are probably due to increased recruitment of blood monocytes to lungs or due to increased local proliferation and survival of lung macrophages. [2, Rank 4]

There are increased numbers of neutrophils in sputum and bronchial lavage in chronic obstructive pulmonary disease and their numbers correlate with disease severity. Chemotactic signals for neutrophil recruitment include leukotriene B4, CXCL1 (previously known as growth-related oncogene [GRO]-α), CXCL2 (GROβ), CXCL3 (GROγ), CXCL5 (epithelial neutrophil-activating peptide 78), and CXCL8, the expression of which is increased in chronic obstructive pulmonary disease and likely to be derived from alveolar macrophages and epithelial cells. GM-CSF and granulocyte CSF may increase the survival of neutrophils.

There is now increasing interest in the participation of the inflammasome in chronic obstructive pulmonary disease, which could be the origin of some cytokines. The inflammasome's primary role is defending against invading pathogens, including bacteria and viruses. The innate immune system is characterized by its ability to recognize and respond to an array of infectious agents and endogenous molecules (as shown in figure 5), such as double-stranded deoxyribonucleic acid and extracellular adenosine triphosphate

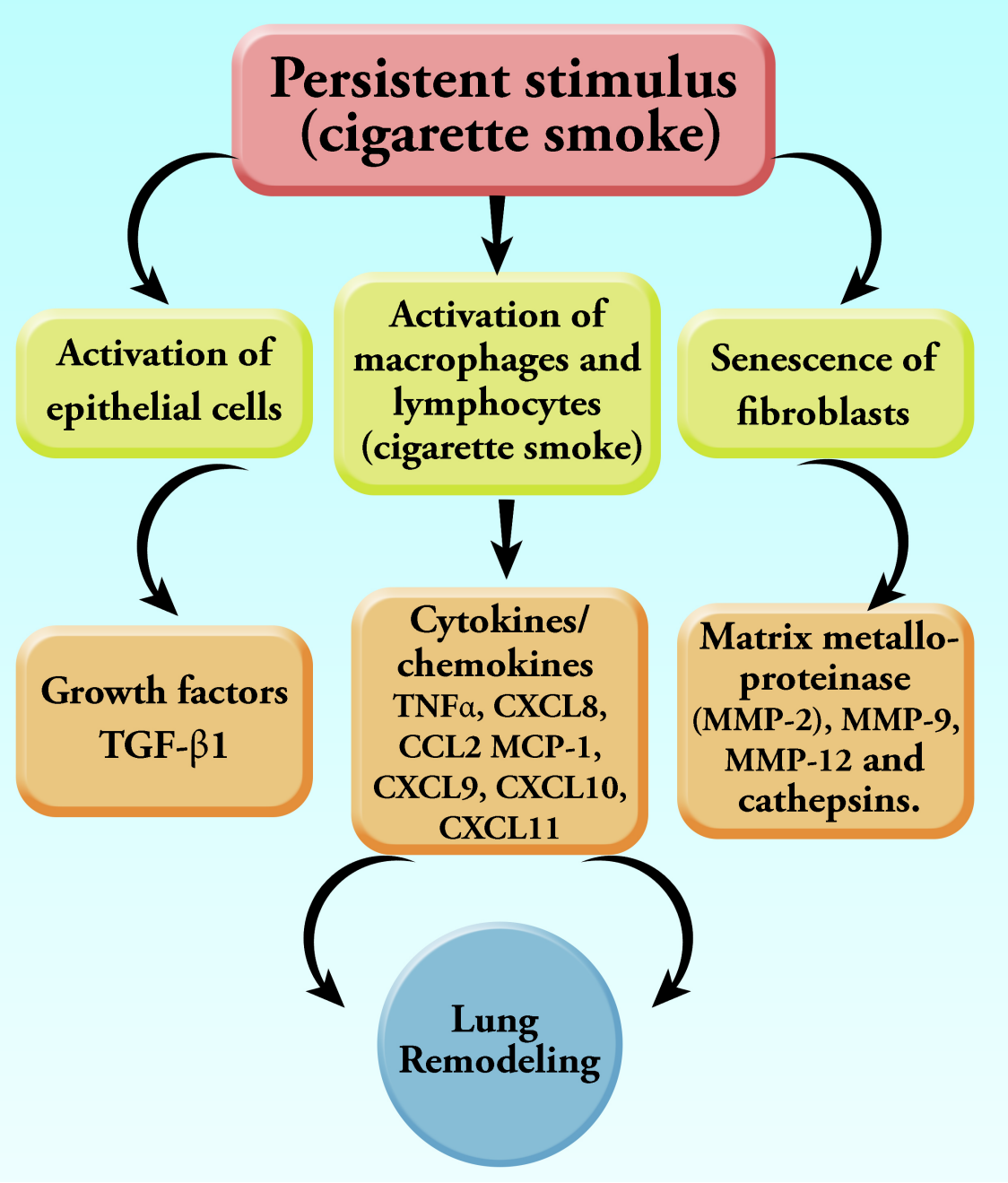


Figure 4: Examination of the client

released during cell and tissue injury. This is mediated through the detection of these pathogen-associated and danger-associated molecular patterns by receptors termed pattern-recognition receptors. These include the Toll-like receptors (TLRs), the intracellular retinoic acid-inducible gene-like helicases and the intracellular nucleotide-binding oligomerization domain-like receptors (NLRs).

**"Smoking cessation is the key intervention for all COPD patients who continue to smoke"**

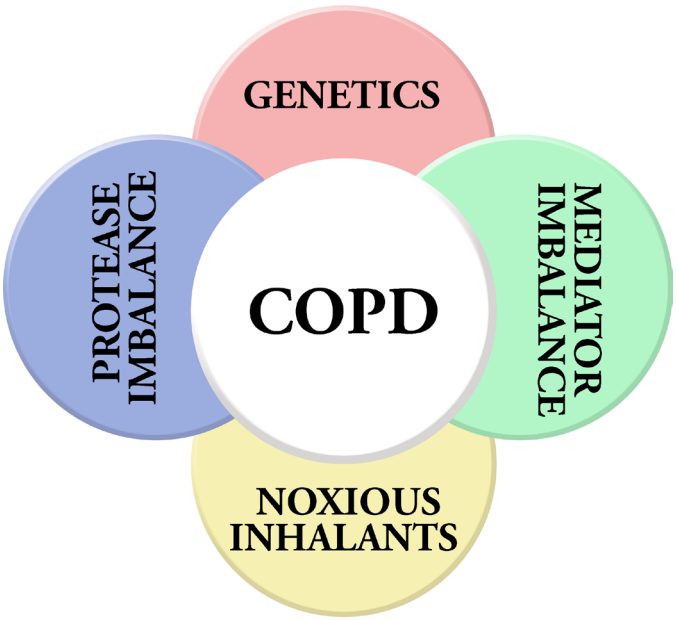


Figure 5: Inflammasome in COPD

NLRs are characterized by three domains, including an N-terminal interaction domain that mediates protein–protein interactions with downstream signalling intermediates and that can be used to categorize the NLRs into five subfamilies (as shown in figure 6) -- NLRA (containing an acidic transactivation domain), NLRB (containing a baculovirus inhibitor of apoptosis protein repeat), NLRC (containing a caspase-recruitment domain), NLRP (containing a pyrin domain), and NLRX (containing an unknown domain).

NLRs respond to pathogen-associated and danger-associated molecular patterns through the formation of inflammasomes: multimeric cytoplasmic protein complexes that act as molecular platforms for the activation of inflammatory caspases following stimulation by foreign

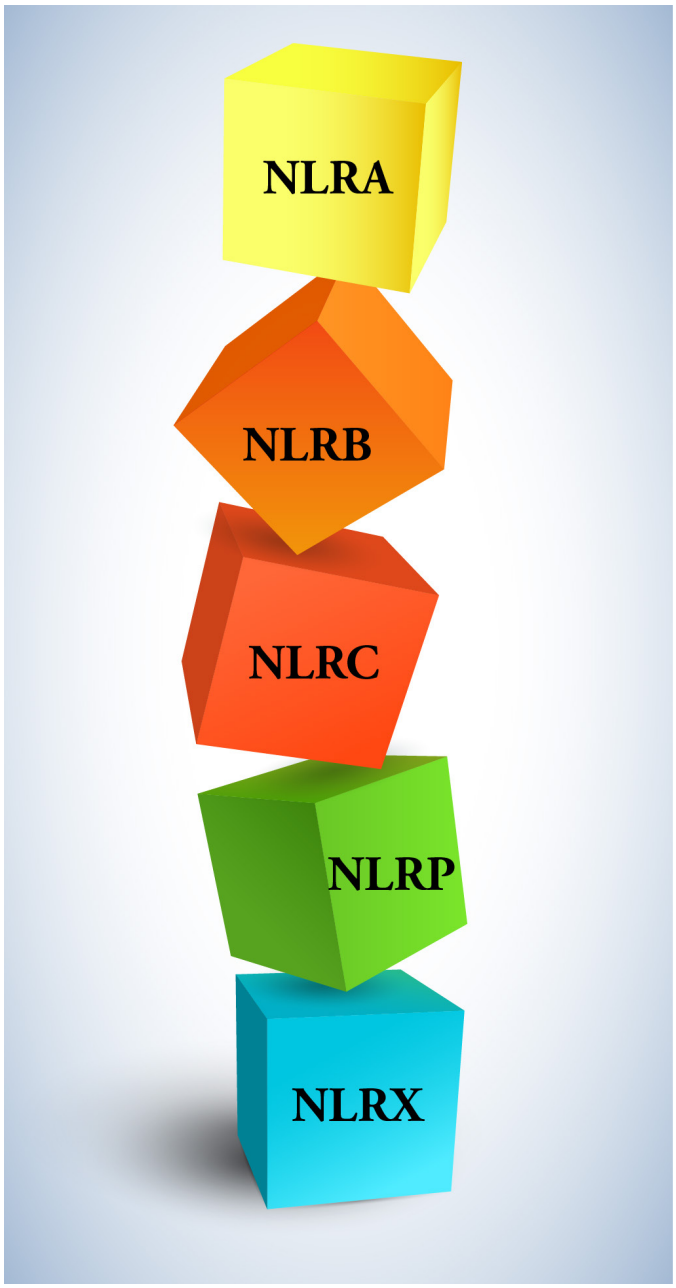


Figure 6: Subfamilies of NLRS

agonists. A typical inflammasome is composed of an NLR, an adaptor protein, such as apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) and an effector caspase that activates proinflammatory cytokines, in particular IL-1β and IL-18. Three NLR proteins have been shown to form inflammasomes: NLRP1, NLRP3 also known as

> "Primary role of inflammasome's is defending against invading pathogens, including bacteria and viruses."

cryopyrin or pyrin-containing Apaf 1 -like protein 1), and NLRC4 (also known as Ipaf) (as shown in figure7).

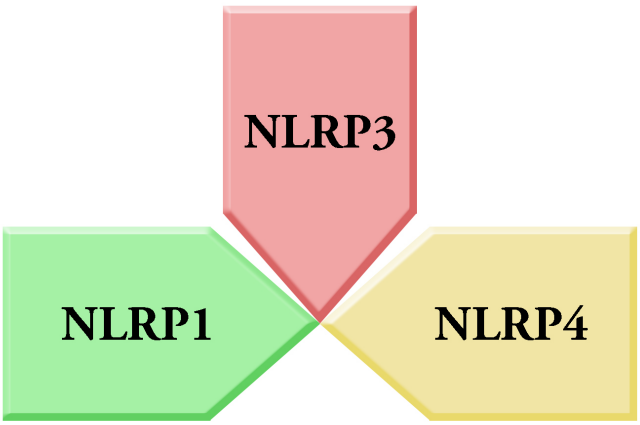


Figure 7: NLR proteins forming inflammasomes

Stimulation of the NLRP3 leucine-rich repeat domain by a foreign agonist is postulated to unfold the NLRP3 molecule, enabling recruitment of the ASC adaptor proteins and procaspase 1. Thus, the inflammasome acts as a platform for the autoproteolytic cleavage of procaspase 1 to produce active caspase 1, which in turn cleaves pro-IL-1β and pro-IL-18 to promote their secretion in conjunction with the alarming high-mobility group. In chronic obstructive pulmonary disease, there is evidence of an increase in the number of CD8 T-cells expressing TLRs 1,

> "CD8+ T lymphocytes are known to play a critical role in the pathogenesis of COPD"

2, 4, 6, and TLR2/1, with only TLR2/1 increased on lung CD4 T-cells and TLR2 on CD8 natural killer T-cells. There is evidence that TLRs are involved in the release of cytokines, such as IL-12 and IL-17 from T-cells. [3, Rank 3]

There is a very long list of cytokines and chemokines that have been implicated in the many facets of the pathogenesis of chronic obstructive pulmonary disease. Some of these have been supported through genome-wide association studies on chronic obstructive pulmonary disease, lung function and chronic obstructive pulmonary disease complications. Proinflammatory cytokines of importance include TNF α, IFNγ, IL-1β, IL-6, IL-17, IL-18, IL-32, and thymic stromal lymphopoietin (TSLP). [4, Rank 5]

## Aim of pharmacological therapy in Chronic obstructive pulmonary disease

Pharmacological therapy for chronic obstructive pulmonary disease is used to reduce symptoms, reduce the frequency and severity of exacerbations and improve exercise tolerance and health status

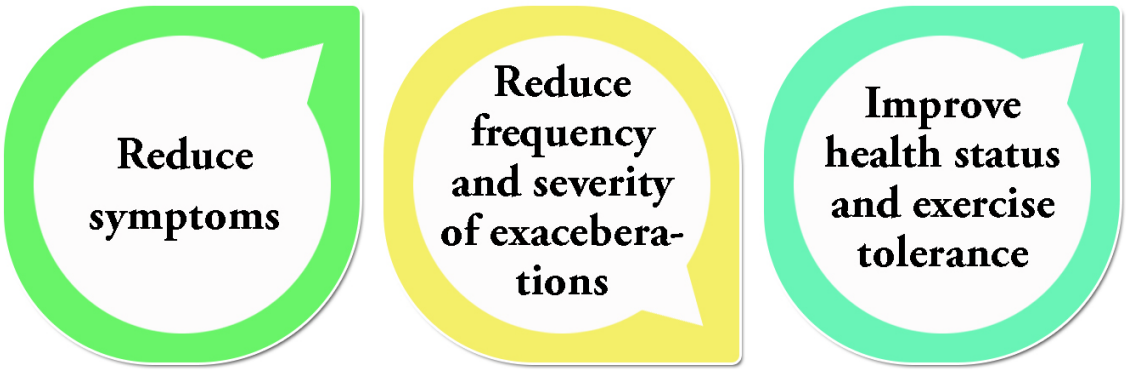


Figure 8: Aim of pharmacological therapy in COPD

(as shown in figure: 8). Long acting bronchodilator therapy is the cornerstone treatment for most patients with chronic obstructive pulmonary disease, for some patients with mild disease and low symptom burden, short acting bronchodilators may suffice for symptom control, but in many cases they should be used only as rescue medications. Inhaled long acting β 2-agonists and long acting anticholinergic (or antimuscarinic) bronchodilators are regularly used for maintenance treatment. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk effects compared with higher doses of monocomponents.

## Long-Acting Bronchodilators

Two key classes of bronchodilators (as shown in figure 9, 10) have been developed in chronic obstructive pulmonary disease: β2-agonists and muscarinic antagonists.

`Short-acting bronchodilators, such as ipratropium, albuterol, and metaproterenol, have formed the cornerstone of initial chronic obstructive pulmonary disease therapy for the past two decades. Subsequently, long-acting bronchodilators were developed (as shown in figure 11).

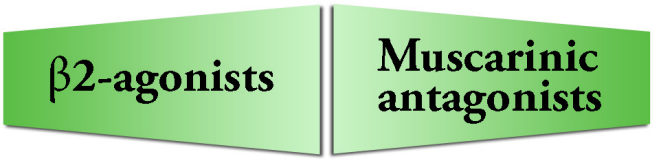


Figure 9: Main types of bronchodilators

The twice-daily long-acting beta agonists salmeterol and formoterol first became available for maintenance therapy of chronic obstructive pulmonary disease more than 15 years ago, while the once-daily long-acting muscarinic antagonist tiotropium has been available for 10 years and is the most widely prescribed maintenance monotherapy bronchodilator in chronic obstructive pulmonary disease. Inhaled bronchodilators, as monotherapy or in combination,

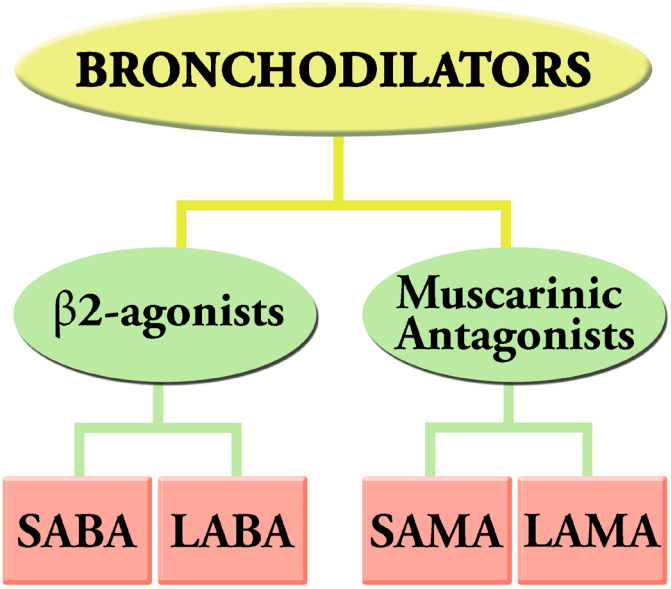


Figure 10: Classification of bronchodilators

remain the mainstay for patients in all categories. Long-acting bronchodilators, such as tiotropium, formoterol, and salmeterol, are proven to provide long-term improvements in lung function, quality of life, and exacerbations in patients with chronic obstructive pulmonary disease. Long-acting bronchodilators (e.g., tiotropium, salmeterol) also reduce lung hyperinflation and dyspnea and increase exercise endurance. The once-daily long-acting beta agonist indacaterol, the once-daily long-acting muscarinic antagonist glycopyrronium, and twice-daily long-acting muscarinic antagonist aclidinium represent newer, recently licensed therapies and there are also several once-daily long-acting beta agonists and long-acting muscarinic antagonists in development, including olodaterol, vilanterol, and glycopyrrolate. [5, Rank 3]

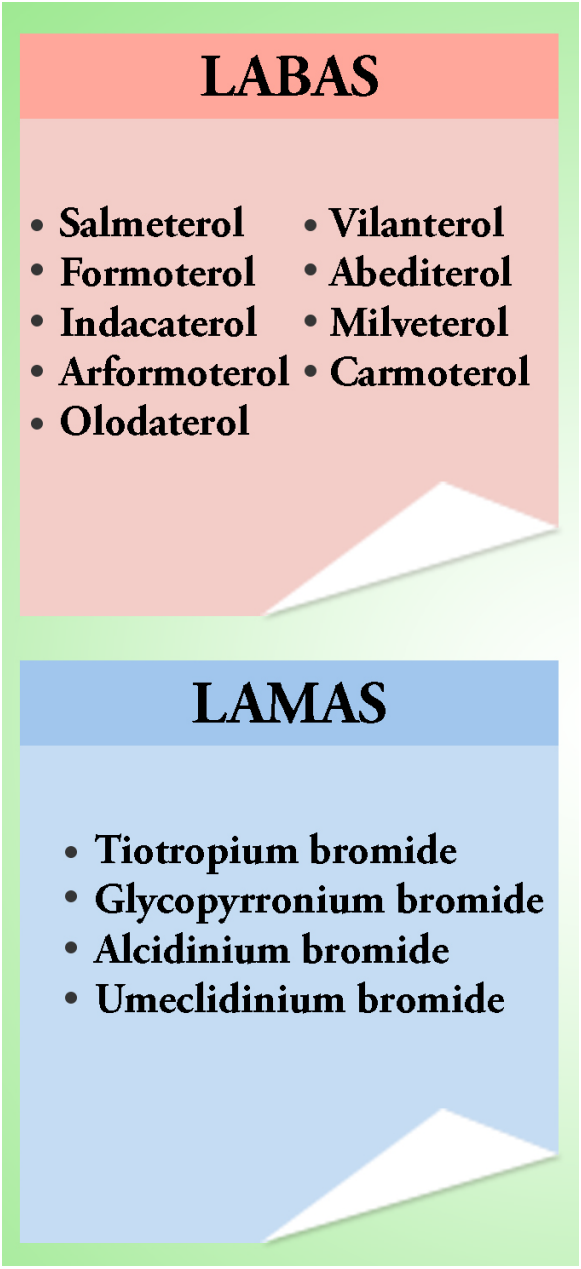


Figure 11: Examples of long acting bronchodilators

## Combination Bronchodilation

Dual bronchodilation improves lung function compared with a single bronchodilator

> "Combination therapy has the potential to improve outcomes when compared to monotherapy"

## Rationale

Guidelines recommend combination therapy involving two long-acting bronchodilators with differing modes of action in patients whose chronic obstructive pulmonary disease is not sufficiently controlled with monotherapy. Airway smooth muscle relaxation (leading to bronchodilation) can be achieved via two main routes (Figure: 12):

- Inhibition of acetylcholine signaling via muscarinic M3 receptors on airway smooth muscle with a muscarinic antagonist
- Stimulation of β2-adrenoceptors with a β2-agonist.

Targeting these two mechanisms of bronchoconstriction, theoretically, has the potential to maximize the bronchodilator response without increasing the dose of either component and helps to overcome the inter- and intra-patient variability in response to individual agents seen in chronic obstructive pulmonary disease. However, β2-agonists can amplify the bronchial smooth muscle relaxation directly induced by the muscarinic antagonist by decreasing the release of acetylcholine via modulation of cholinergic neurotransmission. Additionally, muscarinic antagonists have been

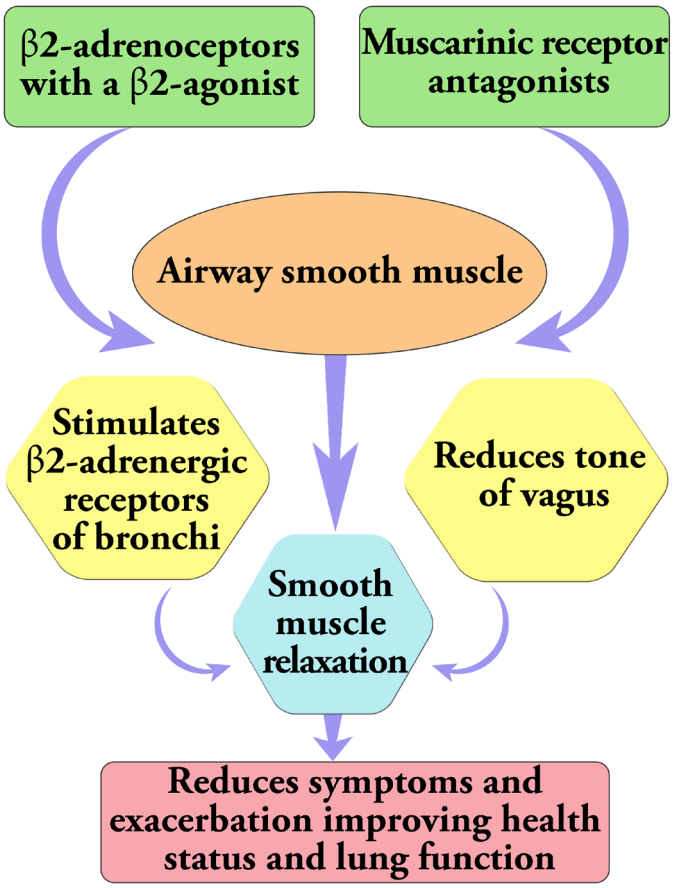


Figure 12: Mode of action with combination therapy

demonstrated to augment β2-agonist-stimulated bronchodilation by reducing the bronchoconstrictor effects of acetylcholine in preclinical models.

The rationale for improved bronchodilation has been tested in preclinical models with a specific investigational long-acting muscarinic antagonist / long-acting beta agonist combination, (as shown in figure 13) tiotropium plus olodaterol, demonstrating synergistic effects on bronchoprotection in vivo. Combination treatment in ovalbumin-induced bronchoconstriction in anesthetized guinea pigs has demonstrated improved bronchoprotection in a dose-dependent manner, with

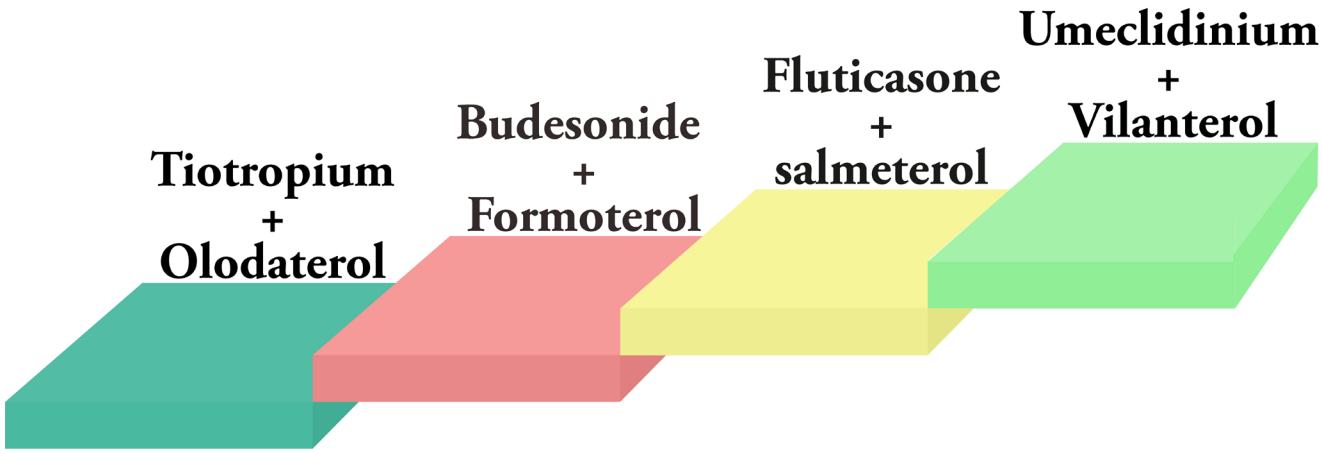


Figure 13: Combination bronchodilators

effective dose (ED) 50 values 10-fold lower than the ED 50 of olodaterol alone ($p < 0.05$); similar results were reported versus tiotropium monotherapy in acetylcholine-induced bronchoconstriction in anesthetized dogs. Indacaterol synergistically potentiates the effects of glycopyrronium to inhibit metacholine-induced contraction of airway smooth muscle in vitro. However, specifically designed clinical studies are required to assess whether such synergistic effects can be observed with therapeutic doses in humans. [6, Rank 4]

## Short-acting muscarinic antagonist plus short-acting β2-agonist

The concept of adding a muscarinic antagonist to a β2-agonist is by no means new. These medications work quickly to decrease shortness of breath. A fixed-dose combination (FDC) of the short-acting agent's (as shown in figure: 14) ipratropium and albuterol, offenoterol and ipratropium clearly provides benefits over monotherapy with either component. Additionally, dual bronchodilation with ipratropium and albuterol resulted in a consistently longer response and more patients achieved a pre-specified response level (12-15%) in forced expiratory volume in 1 second (FEV1) with the combination versus individual components ($p<0.05$), with an equivalent or improved safety profile.

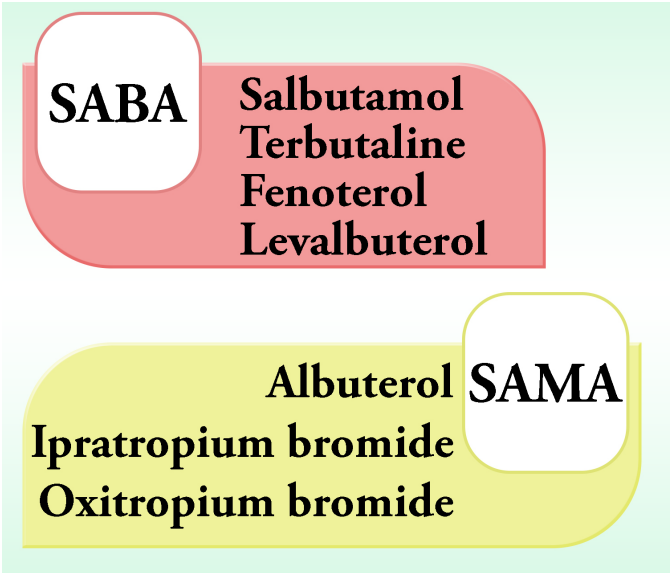


Figure 14: Examples of SABA and SAMA

"The most commonly used SABA is salbutamol, the onset of action is within 3 minutes"

## Free combinations of LAMA plus LABA

Relatively few studies have examined the combination of long-acting muscarinic antagonists and long-acting beta agonists. Until recently, research focused on free combinations of existing therapies and has demonstrated benefits on lung function and other outcomes. Following proof of concept in terms of a benefit on FEV1 and in patients with acute exacerbations, several randomized controlled trials have reported improved lung function for tiotropium plus formoterol versus tiotropium alone. Some trials have also identified significant improvements in symptom scores and reductions in rescue medication use. A recent meta-analysis confirmed the benefits of tiotropium plus formoterol on average FEV1, trough FEV1, and Transition Dyspnea Index (TDI), with initial reports also suggesting that the combination may provide statistically significant improvements in effort-induced dynamic hyperinflation and exercise tolerance.

Currently available data on tiotropium plus salmeterol are conflicting. Initial investigations indicated the benefits of tiotropium plus salmeterol versus either monotherapy alone, while suggesting co-administration of once-daily salmeterol plus tiotropium was inadvisable, due to the shorter duration of bronchodilation provided by salmeterol. The Canadian Optimal Therapy of chronic obstructive pulmonary disease trial investigated the impact of tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus salmeterol/fluticasone on clinical outcomes in 449 patients with moderate to severe chronic obstructive pulmonary disease. Tiotropium plus salmeterol/fluticasone (but not tiotropium plus salmeterol) statistically improved lung function and quality of life, while no improvement in overall exacerbation rate was seen, it reduced the number of hospitalizations for exacerbations compared to tiotropium plus placebo. A more recent study, however, demonstrated significant improvements in FEV1 with salmeterol once or twice daily plus tiotropium and the combination was also associated with clinically significant improvements in Transition Dyspnea Index. These inconclusive data suggest that further research is necessary to determine any advantage of salmeterol plus tiotropium. Initial investigation of other free combinations has also been reported; tiotropium plus indacaterol

> "Dual bronchodilator therapy with a long-acting muscarinic antagonist and long-acting beta agonist has the potential to treat the symptoms of COPD and improves lung function"

has been demonstrated to improve lung function and inspiratory capacity, as well as providing a further reduction in use of rescue medication. The long-acting muscarinic antagonist GSK233705 twice daily plus salmeterol has also demonstrated significantly improved trough FEV1 from baseline compared to monotherapy. Overall, these data broadly confirm that combination therapy has the potential to improve outcomes versus monotherapy and justify further research in this area. [7, Rank 3]

## Fixed Dose Combinations

Fixed-dose combinations of long-acting muscarinic antagonists and long-acting beta agonists offer the potential of improved convenience and compliance over use of separate inhalers and during their development, the dose of each agent to be used in combination can be optimized. A major challenge associated with development of fixed-dose combinations is provision of improved bronchodilation over monotherapy components while balancing the associated adverse effects. Dose-finding studies are required to establish minimal effective doses for each agent in the combination, as it cannot be assumed that these doses are the same as would be used in monotherapy. [8, Rank 5]

A number of fixed-dose combinations are in development, (as shown in figure 15) with substantial clinical programs and some Phase II/III results are available. In all cases, there is evidence of improved lung function parameters with the combinations versus monotherapy components. Glycopyrrolate/ glycopyrronium are being developed as part of two combinations: the former plus formoterol as a twice-daily combination and the latter plus indacaterol as a once-daily combination. Glycopyrrolate plus formoterol has recently reported improvements in FEV1 area under the curve from 0–12 hours (AUC0-12) versus monotherapy with glycopyrrolate, formoterol, or tiotropium and in inspiratory capacity versus tiotropium monotherapy. Indacaterol is approved at doses of 150 and 300 µg in the EU and 75 µg in the US. Early studies investigated high doses of indacaterol in combination with glycopyrronium, but the recent SHINE, ILLUMINATE and ENLIGHTEN studies have examined the effects of indacaterol (110 µg) plus glycopyrronium (50 µg). The SHINE study reported significantly greater improvements in trough

FEV1 after 26 weeks' treatment with the combination compared to monotherapy with indacaterol (mean difference 70 mL), glycopyrronium (90 mL), or tiotropium (80 mL). This study also demonstrated improvements in dyspnea (versus placebo and tiotropium), St George's Respiratory Questionnaire (versus placebo) and reduced use of rescue medication (versus placebo and all monotherapies). The ILLUMINATE study has provided interesting information on the relative effects on lung function of a long-acting beta agonist / long-acting muscarinic antagonist combination versus long-acting beta agonist/ inhaled corticosteroids (ICS): significant sustained and clinically meaningful improvements in trough FEV1, peak FEV1, and FEV1 AUC0-12 with indacaterol plus glycopyrronium versus the long-acting beta agonists/ ICS salmeterol/ fluticasone ($p < 0.001$ for all comparisons). Mean treatment difference for indacaterol plus glycopyrronium versus salmeterol/ fluticasone ranged from 103 mL (trough FEV1) to 155 mL (peak FEV1). Additionally, the longer-term ENLIGHTEN study reported significant improvements in lung function with the combination versus placebo sustained for 52 weeks, with no evidence of tachyphylaxis. [9, Rank 4]

Clinical Phase II trials have investigated the optimal dosing for olodaterol

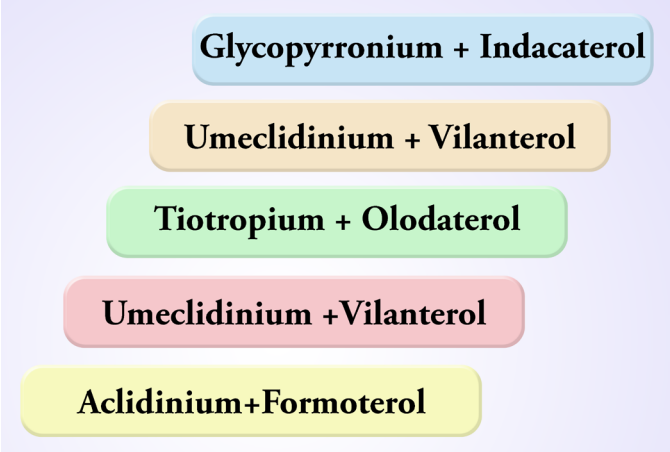


Figure 15: Fixed dose combinations

added to a fixed dose of tiotropium and for tiotropium added to a fixed dose of olodaterol. Significant improvements in peak FEV1 were demonstrated with tiotropium/ olodaterol 5/2 µg ($p=0.008$), 5/5 µg ($p=0.012$), and 5/10 µg ($p<0.0001$) versus tiotropium monotherapy. Significant improvements were also seen in trough FEV1 with tiotropium/ olodaterol 5/10 µg versus tiotropium monotherapy ($p=0.034$), and with all doses of the combination tested versus olodaterol monotherapy with evidence of dose ordering.

Of the long-acting muscarinic antagonist/ long-acting beta agonist's fixed-dose combinations currently under investigation, tiotropium plus olodaterol, umeclidinium plus vilanterol, aclidinium plus formoterol, and glycopyrronium plus indacaterol have the largest Phase III programs, focusing on efficacy, safety, exacerbations, exercise, and dyspnea. The development program for umeclidinium plus vilanterol

> "Bronchodilators are a cornerstone of COPD treatment Short acting bronchodilators are an option for patients with occasional dyspnea, at low risk of exacerbations"

involves four large pivotal trials, one large safety study, and two studies assessing exercise endurance, with two ongoing trials investigating lung function and efficacy. Phase III studies of glycopyrronium plus indacaterol will compare the combination with a range of comparators, including fluticasone/salmeterol combination and tiotropium, across a variety of end points (FEV1, exacerbations, TDI, and safety). The tiotropium plus olodaterol development program includes two main registration trials, three examining exercise and functional capacity, one examining long-term safety and a comprehensive lung function trial.

Several of the long-acting muscarinic antagonist/ long-acting beta agonists/ fixed-dose combinations in development will be delivered once daily (such as umeclidinium plus vilanterol and tiotropium plus olodaterol) while others will have twice-daily dosing (e.g., aclidinium plus formoterol). This diversity has the potential to increase the personalization of medication to individual needs; for instance, twice-daily combinations could be considered where patients suffer from night-time symptoms, while once-daily combinations may be prescribed to improve adherence. [10, Rank 5]

## Patient and Physician Perceptions

While a substantial body of evidence demonstrates the importance and impact of symptoms to patients, patient and physician perceptions of this impact may not always correspond. Overall, patients appear to underestimate their morbidity and are possibly undertreated as a result. Based on an objective breathlessness scale, in patients classified as too breathless to leave the house, a third described their condition as mild to moderate. In another study, while both physicians and their patients identified breathlessness, fatigue, and coughing as the main symptoms of chronic obstructive pulmonary disease that had most effect on patients' lives, within the other symptom categories, such as expectoration, dry mouth, despondency, wheezing, sleeping difficulties and chest pain, there were varying perceptions (in terms of rank) of the impact of these symptoms. There was a greater degree of physician-patient concordance in patients with more severe chronic obstructive pulmonary disease.

Another study observed good concordance between the frequencies of night-time symptoms reported by patients and physicians, but also found that physicians significantly underestimated the impact of chronic obstructive pulmonary disease symptoms on patients' lives.

As current treatment options still lack control over symptoms, there remains a need for additional therapies. The exploration of treatment options that target both airway obstruction and chronic obstructive pulmonary disease symptoms throughout the 24-h day may therefore provide patients with relief from the substantial impact that these symptoms can have on their health status. [11, Rank 4]

## Pharmacologic Therapy to Prevent COPD Exacerbations

Pharmacological therapy for chronic obstructive pulmonary disease is to reduce symptoms, reduce the frequency and severity of exacerbations. Characterizing chronic obstructive pulmonary disease phenotypes may identify patients who will respond better to a specific type of treatment and thereby individualize therapy. Combining bronchodilators with different mechanism and durations of action may increase the degree of bronchodilation with a low risk of side effects compared to increasing the dose of a single bronchodilator (as shown in figure 16). Unfortunately, clinical trial inclusion criteria do not always match the phenotypes of patients used by guidelines. For example, exacerbation frequency may not be specified as an inclusion criterion, or if exacerbation criteria are specified, the frequency (≥1) may be different than those specified by guidelines (≥2).

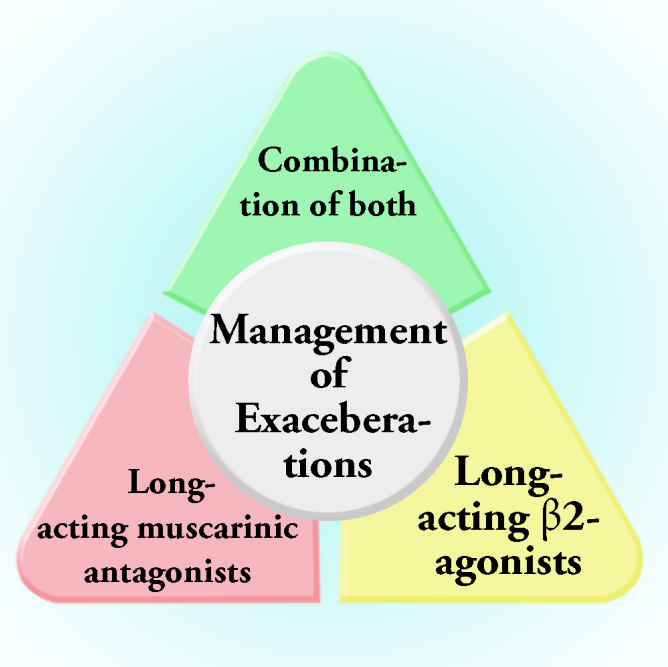


Figure 16: Management of exacerbations

## Long Acting Bronchodilators

Bronchodilation with long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs) alone or in combination, is a recommended treatment option for most patients with chronic obstructive pulmonary disease. Long-acting bronchodilators reduce exacerbation risk by improving expiratory airflow when patients

are stable; thereby decreasing air trapping that develops during an exacerbation.

Several studies have demonstrated the efficacy of long-acting bronchodilators in reducing exacerbation risk in populations of patients with or without a history of exacerbations. Some of these studies have specifically recruited patients with a history of ≥1 exacerbation in the previous year, in order to "enrich" the population with patients more likely to exacerbate during the study period. Long-acting bronchodilators reduce exacerbation rates compared with placebo both in these "enriched" populations and in studies where there were no specific inclusion criteria regarding exacerbation history. This demonstrates the broad ability of long-acting bronchodilators to prevent future exacerbations irrespective of previous exacerbation history.

Long-acting beta agonists monotherapy with salmeterol has been shown to reduce the annual rate of moderate or severe exacerbations by 15 % compared with placebo ($p < 0.001$) in a population of patients that may or may not have a history of exacerbations and by 20 % compared with placebo ($p = 0.003$) in patients with more than one exacerbation in the prior year. Other long-acting beta agonists seem to be effective at reducing exacerbations and in a post-hoc pooled analysis of 6-month data from three large Phase III trials of indacaterol 150 and 300 µg once daily versus placebo in 2716 patients with moderate-to-severe chronic obstructive pulmonary disease, exacerbation rates were significantly reduced by about 30 % with both doses of indacaterol (rate ratios: 0.69; 95 % confidence interval [CI] 0.55, 0.87 and 0.71; 95 % CI 0.57, 0.88, respectively; both $p = 0.002$). [12, Rank 2]

> **"Long acting bronchodilators (as monotherapy or in combination) are used in acute exacerbations.**
>
> **Combining bronchodilators with different mechanism and durations of action may increase the degree of bronchodilation with a low risk of side effects compared to increasing the dose of a single bronchodilator."**

The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial in patients with stable chronic obstructive pulmonary disease demonstrated a 14 % reduction in exacerbations with tiotropium 18 µg once daily versus usual treatment at 4 years' follow-up ($p < 0.001$). In a recent systematic review of 22 studies and >23,000 patients with stable chronic obstructive pulmonary disease, which included UPLIFT,

UPLIFT, tiotropium was associated with a 22 % reduction in exacerbations versus placebo (OR 0.78; 95 % CI 0.70, 0.87). Other long-acting muscarinic antagonists have also demonstrated efficacy on exacerbations. In the GLOW 1 and 2 studies, where ~95 % of patients had an exacerbation history of 0 or 1 at baseline, glycopyrronium significantly reduced the risk of first moderate or severe exacerbation (by 31 %, $p<0.05$) and the rate of moderate or severe chronic obstructive pulmonary disease exacerbations (by 34 %,$p=0.001$) versus placebo. Data on exacerbations with aclidinium are mixed, with one study showing fewer patients experiencing a moderate or severe exacerbation (hazard ratio [HR] 0.7; 95 % CI 0.55, 0.90; $p = 0.0046$) compared with placebo and another study showing no effect, although the overall exacerbation rate was low, which can reduce the ability to detect an effect of treatment. Studies specifically in patients with prior exacerbations suggest that long-acting muscarinic antagonists may be more effective than long-acting beta agonists at reducing the risk of exacerbations. For example, in the Prevention Of Exacerbations with Tiotropium in chronic obstructive pulmonary disease (POET-COPD) study, which included patients having had at least one exacerbation requiring treatment or hospitalization in the previous year, tiotropium significantly reduced the risk of exacerbations by 17 % versus salmeterol ($p< 0.001$). Genotyping of a subgroup of patients in this study highlighted that polymorphisms of the β2-adrenoceptor can affect exacerbation outcomes in response to salmeterol but not tiotropium, and this may have contributed to the difference between treatments in exacerbations. [13, Rank 4]

Data are emerging on the benefits of long acting beta agonists/ long-acting muscarinic antagonist combination therapies in reducing the risk of exacerbations versus various comparators. In a pooled analysis of two 6-month randomized trials, aclidinium/ formoterol (long-acting beta agonist/ long-acting muscarinic antagonist fixed combination) reduced the rate of moderate or severe exacerbations by 29 % compared with placebo ($p<0.05$). In the SPARK study of 2224 patients with GOLD stages 3–4 chronic obstructive pulmonary disease and ≥1 moderate chronic obstructive pulmonary disease exacerbation in the past year, indacaterol/ glycopyrronium (IND/GLY) significantly reduced the rate of moderate-to-severe exacerbations by 12 % ($p= 0.038$) and all exacerbations by 15 % ($p= 0.0012$) compared with glycopyrronium monotherapy. In addition, IND/GLY

reduced the risk of all exacerbations vs tiotropium monotherapy (14%;p=0.0017) and had a trend to a reduction in the risk of moderate-to-severe exacerbations (10 %; p =0.096). Recently, the LANTERN study of 744 patients with moderate-to-severe chronic obstructive pulmonary disease and one or no exacerbations in the previous year reported a significant 31 % reduction in the rate of moderate or severe exacerbations (an exploratory endpoint) with IND/GLY compared with salmeterol/ fluticasone propionate (SFC) ($p<0.05$). The FLAME study has investigated the effect of IND/GLY compared with salmeterol/ fluticasone propionate on exacerbations as the primary outcome in a population of 3362 patients with a history of exacerbations, and demonstrated that IND/GLY was more effective than salmeterol/ fluticasone propionate for reducing the rate of all exacerbations by 11 % ($p = 0.0003$) and moderate or severe exacerbations by 17% ($p < 0.001$). Moreover, although the annual rate of severe exacerbations did not reach statistical significance between the two treatment arms due to the low number of events, the time to first severe exacerbation was significantly longer with IND/GLY compared with salmeterol/ fluticasone propionate (19 % lower risk, $p = 0.046$).

Much data are available demonstrating the effectiveness of long-acting bronchodilators in terms of exacerbation reduction in patients with chronic obstructive pulmonary disease, with studies showing rate reductions compared with placebo of up to 20–30 % with long-acting beta agonists and 34–35 % with long-acting muscarinic antagonists. Interestingly, combining a long-acting beta agonist and long-acting muscarinic antagonist results in a reduction of risk compared with a long-acting muscarinic antagonist alone and more importantly, a significant reduction of exacerbation risk compared with long acting beta agonists/inhaled corticosteroids. [14, Rank 4]

## Inhaled Corticosteroids and Long Acting Bronchodilators

Inhaled corticosteroids (ICS) are generally licensed in chronic obstructive pulmonary disease for use in combination with a long-acting beta agonist for patients with a history of exacerbations in the past year. GOLD (as shown in figure: 17) recommends that patients with ≥2 exacerbations (or one hospitalization) should be considered for inhaled corticosteroids long-acting beta agonist treatment. The Spanish, the Finnish and Czech guidelines

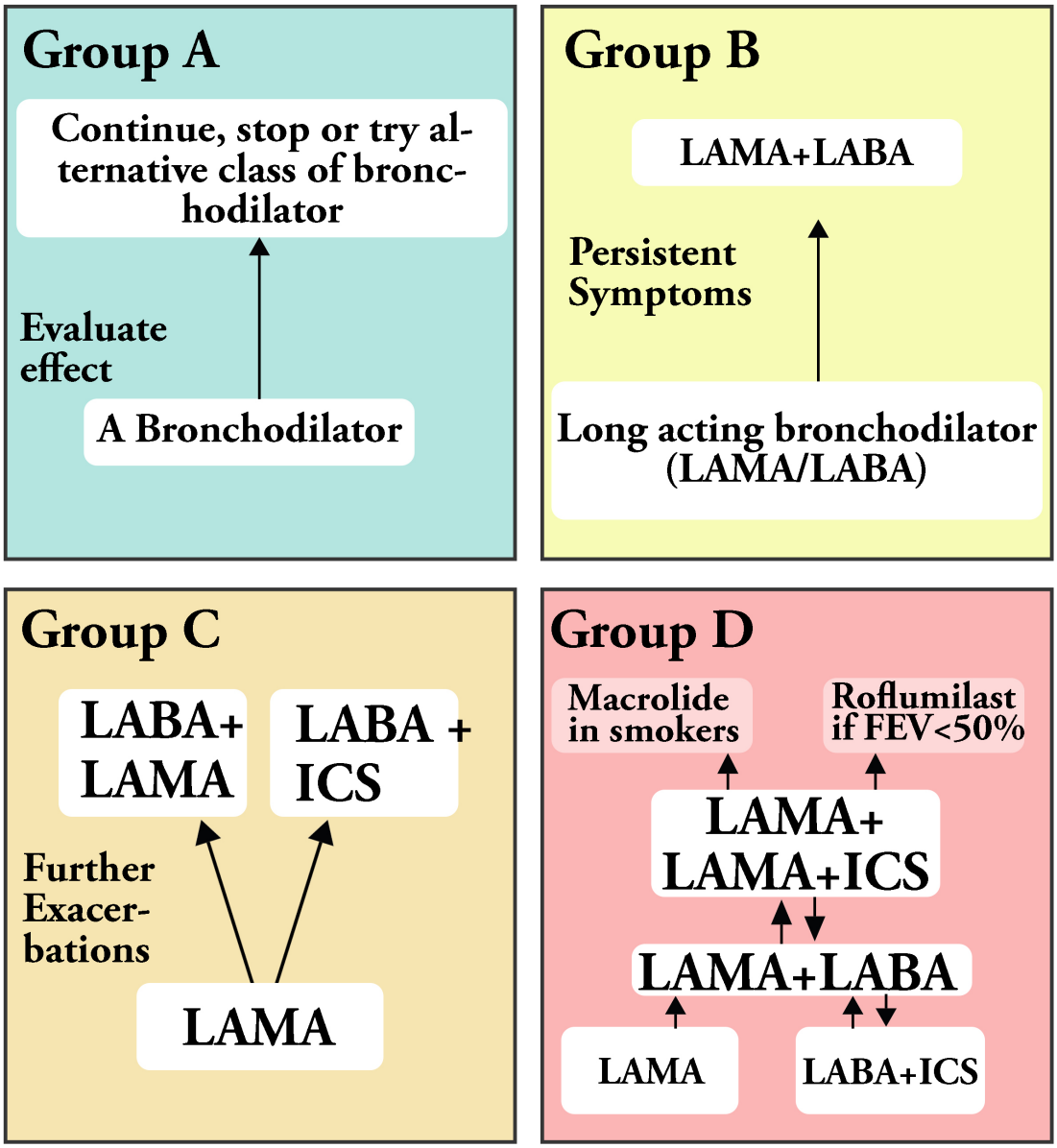


Figure: 17 Pharmacological management based on GOLD criteria

recommend inhaled corticosteroids for patients classified as frequent exacerbators or of the ACOS phenotype.

Although inhaled corticosteroids (as shown in figure 18) alone have been shown to produce modest reductions in the occurrence of exacerbations, their efficacy is enhanced when combined with a long-acting beta agonist, as demonstrated in a Cochrane review and in a Bayesian network meta-analysis. In the Towards a Revolution in Chronic obstructive pulmonary disease Health (TORCH) study, salmeterol/ fluticasone propionate was associated with a 25 % reduction in exacerbation rate versus placebo ($p < 0.001$), a 12 % reduction versus salmeterol ($p = 0.002$) and a 9 % reduction versus fluticasone propionate ($p=0.02$).

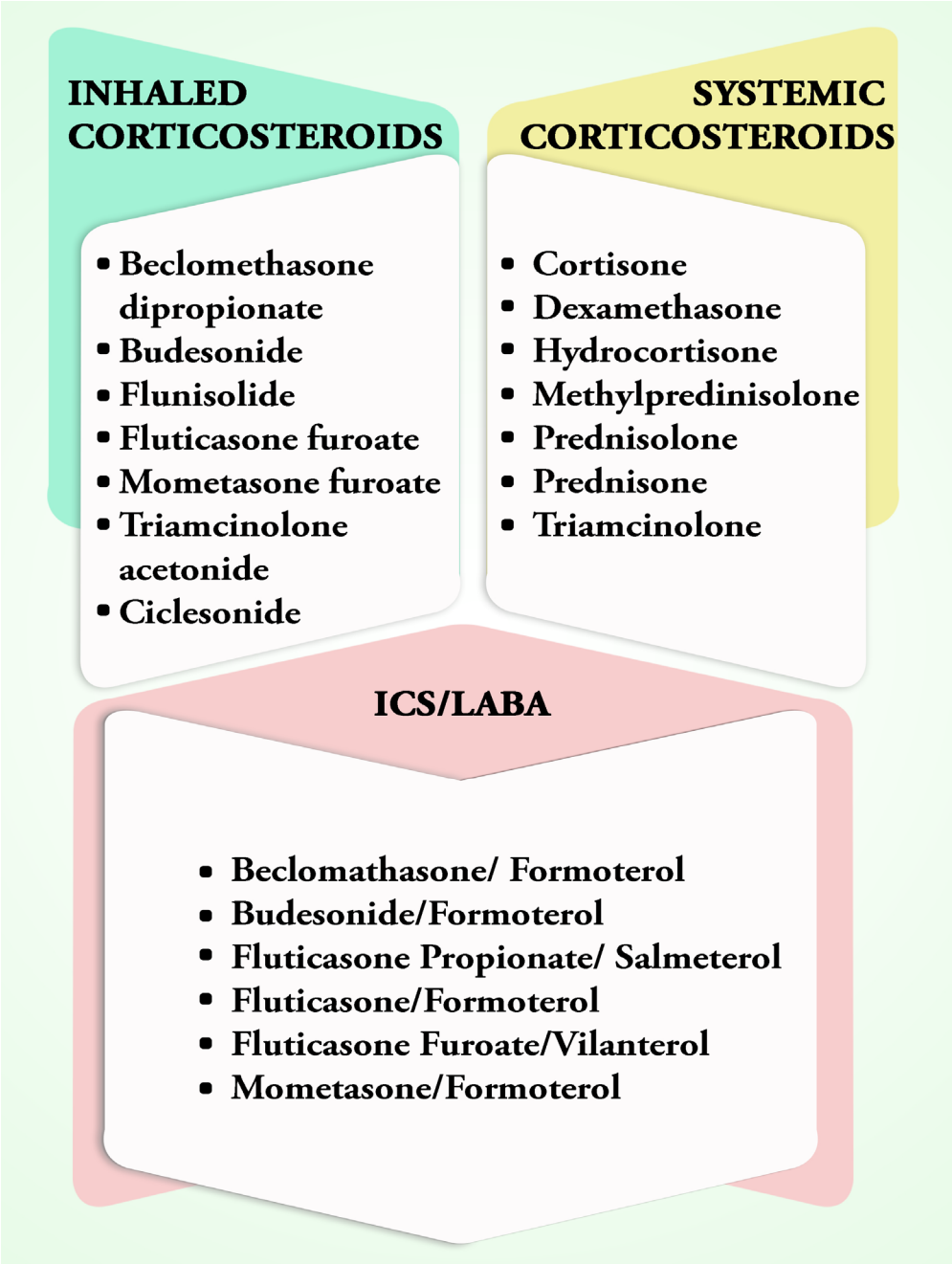


Figure 18: Examples of corticosteroids in management of COPD

Although salmeterol/ fluticasone propionate was more effective than salmeterol monotherapy for reducing the risk of moderate-to-severe exacerbations, there was no significant difference in the risk of severe exacerbations (requiring hospitalization).

Similarly, in a study of 797 patients with chronic obstructive pulmonary disease (FEV1<50 % predicted and at least one exacerbation in the year prior to the study), SFC significantly reduced the annual rate of moderate/ severe exacerbations (30.4 %, $p < 0.001$) versus salmeterol. An analysis of pooled data from two studies in which

participants were given fluticasone furoate/ vilanterol also noted significantly fewer moderate or severe exacerbations compared with vilanterol alone (rate ratio 0.7; 95 % CI 0.6, 0.8; p < 0.0001). In patients with severe airflow limitation (GOLD stage III or IV) and ≥1 exacerbation in the previous year, a combination of budesonide/ formoterol significantly reduced the risk of exacerbations by 28.5, 22.7 and 29.5 % vs placebo, budesonide and formoterol respectively (p < 0.05 for all). In a similar population, budesonide/ formoterol have been reported to reduce severe exacerbations by 24 % vs placebo. [15, Rank 3]

Long-term use of inhaled corticosteroids in patients with chronic obstructive pulmonary disease is associated with an increased risk of pneumonia, fractures and diabetes, among other potential side effects. With questions concerning the long-term safety of inhaled corticosteroids and also data showing similar exacerbation rates with inhaled corticosteroids/ long-acting beta agonist compared with some long-acting bronchodilators, there is emerging consensus that withdrawal of corticosteroids may be appropriate in some patient populations. The WISDOM trial, a 12-month, double-blind, active-controlled study of 2485 patients with severe/ very severe chronic obstructive pulmonary disease and a history

**"Inhaled corticosteroids are central to the management of COPD"**

of exacerbations, showed no increase in the risk of moderate or severe exacerbations in patients who withdrew from inhaled corticosteroids therapy but remained on long-acting beta agonist / long-acting muscarinic antagonist compared with those who remained on inhaled corticosteroids with long-acting beta agonist/ long-acting muscarinic antagonist, although there was an initial drop in FEV1 of approximately 40 mL. Corticosteroid withdrawal without long-acting bronchodilation in severe chronic obstructive pulmonary disease patients may produce a different pattern of results. This observation supports a systematic review of other trials of inhaled corticosteroids withdrawal in which there was no conclusive evidence that withdrawal of inhaled corticosteroids increased exacerbations. Moreover, switching to long-acting beta agonist from long-acting beta agonist/ inhaled corticosteroids has been shown to occur without loss of efficacy or increase in exacerbations in patients with a low risk of exacerbations in the INSTEAD (Indacaterol: Switching Non-exacerbating Patients with Moderate chronic obstructive pulmonary disease from Salmeterol/ Fluticasone to Indacaterol) and OPTIMO (Real-Life

study on the aPpropriaTeness of treatment In MOderate chronic obstructive pulmonary disease patients) studies.

Patients with asthma-chronic obstructive pulmonary disease overlap syndrome may be particularly likely to benefit from inhaled corticosteroids therapy because of the predominance of eosinophilic bronchial inflammation associated with this chronic obstructive pulmonary disease phenotype. In fact, it has been demonstrated that a high Th2 signature in chronic obstructive pulmonary disease correlates with increased airway wall and blood eosinophil counts and greater response of hyperinflation to inhaled corticosteroids in chronic obstructive pulmonary disease patients with Th2 type of inflammation. [16, Rank 5]

The response to inhaled corticosteroids in patients with respiratory disease can be predicted by sputum eosinophil counts. A randomized crossover trial in patients with chronic obstructive pulmonary disease in the absence of clinical diagnosis of asthma demonstrated an improvement in post-bronchodilator FEV1 with inhaled corticosteroids treatment (mometasone furoate) compared with placebo in those patients with the greatest degree of sputum eosinophilia. More recently, two post-hoc analyses have shown that blood eosinophil counts may predict the effects of inhaled corticosteroids/ long-acting beta agonist combination treatment on exacerbation rates. Thus, the identification of patients with eosinophilic inflammation in chronic obstructive pulmonary disease, even in the absence of asthma, may be a useful phenotype to target those most likely to benefit from inhaled corticosteroids therapy, although this approach should be validated in prospective studies first.

> **"Long term treatment with inhaled corticosteroids is recommended with severe COPD and frequent exacerbations that are not adequately controlled by long acting bronchodilators Long-term use of inhaled corticosteroids in patients with chronic obstructive pulmonary disease is associated with an increased risk of pneumonia, fractures and diabetes, among other potential side effects."**

There is little doubt from the studies reviewed that inhaled corticosteroids combined with a long-acting beta agonist is an effective intervention for patients with a history of exacerbations. As shown, such treatment is associated with reductions in

> "Adavir is one of the most commonly used inhalers for the maintenance treatment for COPD. It is a combination of fluticasone, a corticosteroid and salmeterol, a long acting bronchodilator "

exacerbations averaging 25 % compared with placebo and between 23–36 % (12 % if we include the TORCH study) compared with long-acting beta agonist monotherapy. However, there is growing evidence indicating that not all patients with chronic obstructive pulmonary disease respond to inhaled corticosteroids treatment. Given the potential for pneumonia and other important side effects with inhaled corticosteroids in chronic obstructive pulmonary disease populations, emerging data reveal that it may be possible to withdraw the inhaled corticosteroids component in certain patient groups provided that adequate bronchodilation is in place. [17, Rank 2]

## Phosphodiesterase 4 Inhibitors

PDE-4 inhibitors (as shown in figure 19) represent an anti-inflammatory approach that is recognized as a treatment option for patients with chronic obstructive pulmonary disease who are at high risk of exacerbations and have a chronic bronchitis phenotype. In a pooled analysis of two 1-year, placebo-controlled, double-blind, multicenter studies, roflumilast (a PDE-4 inhibitor) was associated with a 17 % reduction in the rate of moderate-to-severe exacerbations compared with placebo in patients with severe chronic obstructive pulmonary disease, chronic bronchitis and a history of previous exacerbation ($p < 0.0003$). A subsequent systematic review of 29 trials with phosphodiesterase-4 inhibitors (15 roflumilast studies, 14 cilomilast studies) has confirmed these observations. More recently, roflumilast was noted to reduce the rate of moderate or severe exacerbations by 13.2 % vs placebo in high-risk patients (severe chronic obstructive pulmonary disease, symptoms of chronic bronchitis and ≥2 exacerbations in the previous year) receiving long-acting beta agonist/ inhaled corticosteroids (of which ~70 % were on triple therapy) in the REACT (Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy) study. Overall, roflumilast is well tolerated with a safety profile consistent with that expected for the phosphodiesterase-4 inhibitor class. The most common adverse events with roflumilast are gastrointestinal in nature, specifically diarrhea, nausea and weight loss.


Figure: 19 PDE4 inhibitors

Psychiatric events (insomnia, anxiety, depression/ suicidal behavior) are also more common with roflumilast in clinical trials. However, studies have demonstrated beneficial effects of roflumilast in terms of glycemic parameters and risk of major adverse cardiovascular events.

Overall, current clinical trial data indicate that the phosphodiesterase-4 inhibitor roflumilast is associated with a reduction in the rate of moderate/ severe exacerbations of 13–17 % when compared with placebo in a subset of patients that exhibit symptoms of chronic bronchitis and are at a high risk of exacerbations despite optimal inhaled therapy. However, tolerance of roflumilast may be a hurdle for more extensive use in severe chronic obstructive pulmonary disease. [18, Rank 5]

**"Phosphodiesterase-4(PDE4) inhibitors are a relatively new class of medicines to improve COPD. They have both bronchodilator and anti-inflammatory effects."**

## Macrolide Antibiotics

The macrolides are bacteriostatic antibiotics with a broad spectrum of activity against many gram positive bacteria (as shown in figure 20). Bacterial infections can trigger chronic obstructive pulmonary disease exacerbations and consequently, long-term antibiotic use has been considered as a strategy for the prevention of exacerbations. A meta-analysis of six randomized controlled trials on the use of prophylactic macrolide antibiotics has reported a 37 % risk reduction for exacerbations compared with placebo.

A systematic review of seven trials covering more than 3000 patients identified a significant effect of continuous antibiotics for reducing the number of patients experiencing an exacerbation (OR 0.55; 95 % CI 0.30, 0.77). Since these analyses, a small study (n=92) confirmed a 42 % decrease in exacerbation rate with maintenance azithromycin treatment compared with placebo (OR 0.58; 95 % CI 0.42, 0.79; p = 0.001) in patients that suffered at least three exacerbations the previous year while on maximal respiratory medications. The continuous use of antibiotics may raise a concern about bacterial resistance and an increase in respiratory pathogens resistant to macrolides has been identified with this

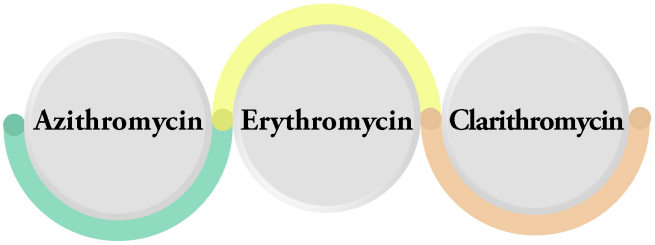


Figure: 20 Macrolide antibiotics

approach in patients with chronic obstructive pulmonary disease.

Long-term use of macrolides has also been linked to hearing loss and gastrointestinal events. Thus, this approach may be best for patients who experience frequent bacterial exacerbations despite optimal treatment with bronchodilators and anti-inflammatory agents and it may be prudent to limit their use to reference centres with adequate follow-up. A post-hoc analysis of patients treated with continuous azithromycin reported that ex-smokers and patients who are older and have milder chronic obstructive pulmonary disease may have a better treatment response. Based on the evidence reviewed here, macrolide antibiotic therapy may be a beneficial strategy for patients who suffer frequent bacterial exacerbations while on maximal bronchodilator therapy, as demonstrated in clinical trials that show reductions in exacerbations ranging from 27 to 42 % compared with placebo. Nevertheless, given the potential for development of bacterial resistance alongside long-term safety concerns, such

> **"Macrolides have immunomodulatory as well as antibacterial effects in COPD"**

treatment needs to be targeted to the most appropriate patient and include careful supervision. [19, Rank 1]

## Mucolytics

Mucolytics (as shown in figure 21) can dissolve thick mucus and are usually used to help relieve respiratory difficulties. They do this by breaking down the chemical bonds between molecules in the mucus. This in turn can lower the viscosity by altering the mucin–containing components. Mucolytic therapies, such as carbocysteine or N-acetylcysteine, may represent an attractive treatment strategy for frequent exacerbators with chronic bronchitis, and particularly those who may be unable to receive inhaled corticosteroids.

A systematic review of 30 trials has reported an increased likelihood of being exacerbation free with mucolytic therapy compared with patients without mucolytic therapy (OR 1.84; 95 % CI 1.63, 2.07). However, it should be noted that there are considerable differences in the patient populations and definitions of exacerbations used in these studies; for example, some of

**MUCOLYTICS**

- N-acetlycysteine(NAC)
- Erdosteine
- Carbocysteine
- Ambroxol
- N-isobutyrylcysteine(NIC)

Figure 21: Mucolytics

> "Mucolytics are oral medications that are believed to increase expectoration of sputum by reducing the viscosity, thus making it easier to cough it up. Improved expectoration of sputum may lead to a reduction in exacerbations of COPD"

these studies were performed in patients with chronic bronchitis, without the requirement for chronic obstructive pulmonary disease to be diagnosed. More recently, a study in 1006 patients with moderate-to-severe chronic obstructive pulmonary disease reported that long-term use of high-dose N-acetylcysteine (600 mg b.i.d.) was associated with a significant decrease in exacerbations compared with placebo (risk ratio 0.78; 95 % CI 0.67, 0.90; p = 0.0011. A smaller study has also confirmed a benefit of high-dose N-acetylcysteine (600 mg b.i.d.) for reducing exacerbations in high-risk patients. Treatment with mucolytics appears to be well tolerated, with similar frequencies of adverse events compared with placebo. Erdosteine, a mucolytic agent with anti-inflammatory, antioxidant and bacterial anti-adhesive properties, has recently been reported to reduce the rate (17 %) and duration (44 %) of exacerbations compared with placebo in patients with chronic obstructive pulmonary disease GOLD stage II-III and at least two exacerbations requiring medical intervention in the previous year.

In summary, while data indicate that the risk of exacerbation is reduced with mucolytic therapies compared with placebo in patients with chronic obstructive pulmonary disease, as demonstrated in an updated systematic review, much heterogeneity exists meaning that current data should be interpreted cautiously. [20, Rank 5]

## LABA

β2-agonists reduce airflow limitation in chronic obstructive pulmonary disease by increasing airway diameter as a consequence of a direct relaxant activity on airway smooth muscle. β2-adrenoceptors occur throughout the airways, principally on airway smooth muscle, but also on a variety of pulmonary cells including

epithelium, submucosal glands, and mast cells. To what extent activation of β 2-adrenoceptors on non-airway smooth muscle cells contributes to reducing airway obstruction in chronic obstructive pulmonary disease remains to be resolved. β2-Agonists can be broadly classified (as shown in figure 22) according to their duration of action; hence short acting beta agonists including salbutamol, terbutaline and fenoterol have pharmacodynamic half-lives between 2–6 h whereas long-acting beta agonist's including salmeterol and formoterol require twice daily treatment, while ultra- long-acting beta agonists(ULAMA), e.g. indacaterol, require once-a-day dosing. Other β2-agonists, which are currently being developed as once-a-day treatment, include vilanterol, olodaterol, carmoterol, abediterol, milveterol and TD-5471.

The clinical effectiveness of these drugs for the treatment of chronic obstructive pulmonary disease is not surprising given their similarities in efficacy in activating the canonical Gs protein pathway leading to elevation of cyclic AMP. These long-acting beta agonist's have similar association and dissociation kinetics for the β 2-adrenoceptor and as a result their long duration of action is attributed to drug efficacy and/ or retention within the airways and close proximity to β2-receptors in

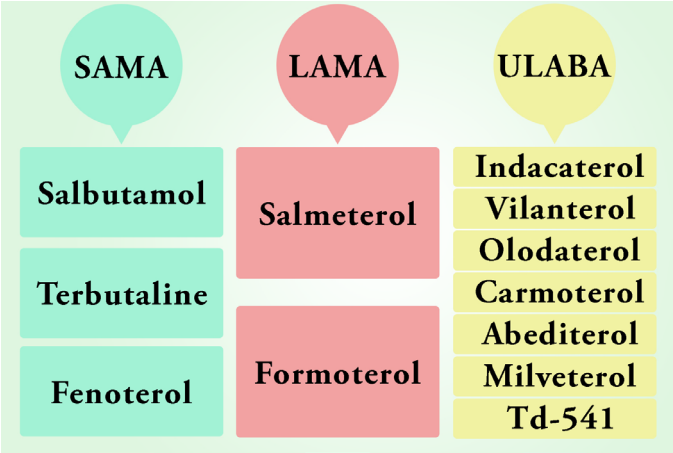


Figure 22: Broad classification of β2-Agonists

airway smooth muscle. Whilst the relative clinical potency of this drug class may differ, there is no demonstrable difference in clinical effectiveness, as exemplified by the different ultra-long-acting long-acting beta agonists in terms of the degree of improvement in lung function. Their utility in the management of chronic obstructive pulmonary disease is clear and numerous clinical studies report improvement in baseline lung function leading to a reduction in residual volume and deflation of the lung which is reflected as improvement in symptoms, quality of life and reduced incidence of exacerbations. [21, Rank 5]

## LAMA

The introduction of tiotropium bromide has proven to be beneficial for the management of chronic obstructive pulmonary disease as shown in clinical trials in terms of improvements in respiratory

symptoms, lung function (FEV1), quality of life and reduction in the frequency of exacerbations. As a consequence other long-acting muscarinic antagonist's including glycopyrronium bromide, aclidinium bromide, umeclidinium bromide and dartropium bromide are in clinical development. This drug class is not generally used in the treatment of asthma, although, tiotropium bromide has been shown to produce bronchodilation of a similar magnitude to salmeterol and proved clinically effective in patients with difficulty to control asthma. The long duration of action of anti-muscarinic drugs has been attributed to a slower off-rate from the M3- receptors versus the M2-receptor; however, it is now recognized that these rate constants have been overestimated as a result of in vitro binding studies undertaken under non-physiological conditions. Their long duration of action has been attributed to high affinity for muscarinic receptors and to retention within the lung following inhalation. Similar to long-acting beta agonists, clinical trials have also shown chronic use of long-acting muscarinic antagonists not only reduces airflow limitation due to the disease, but is also associated with improvements in quality of life, symptom scores and reduced exacerbations. The latter most likely is due to the ability of long-acting muscarinic antagonists to suppress mucus secretion thereby reducing the colonization with bacteria that trigger exacerbation events. [22, Rank 3]

## Combination of LABA/LAMA

There is increasing evidence that long-acting beta agonist/ long-acting muscarinic antagonist combinations can cause greater improvements in airflow limitation than either component drug alone. This might be due to suboptimal doses with either component, and hence, additional bronchodilation afforded by the combination. It has been suggested that β2-receptors that are located pre-junctionally on parasympathetic nerve terminals can suppress acetylcholine release thereby restricting any potential functional competition by acetylcholine at post-junctional muscarinic receptors on airway smooth muscle and submucosal glands occupied by long-acting muscarinic antagonist. Post-junctional M2-receptors on airway smooth muscle are negatively coupled to adenylyl cyclase, hence, a non-selective muscarinic antagonist would inhibit a mechanism which would restrict the ability of long-acting beta agonists to raise intracellular cyclic AMP in airway smooth muscle cells. Such a hypothesis is questionable given the explanation proposed to account for the long duration

of action of long-acting muscarinic antagonists because of more favourable and faster off-rates from pre-junctional M2-receptors. A third possibility is that β2-agonists and long-acting muscarinic antagonists might act synergistically to promote bronchodilation. [23, rank 3]

## Synergy of LAMA/LABA Combination

Synergy is defined as the phenomenon whereby the pharmacological response to two drugs of different classes given in combination exceeds the response that could be explained by their additive effect. Studies investigating the pharmacological effect of combinations of drugs including antimicrobials, chemotherapies and analgesics showed documented evidence of synergism. This phenomenon offers numerous advantages including improvement in clinical effectiveness, reducing the incidence of drug resistance or pharmacological tolerance; and reducing the incidence of side effects of these drugs since potentially lower pharmacological doses of the component drugs can be employed. Whilst synergy is a biological (functional) effect, its evaluation requires a mathematical approach in which the observed effects of drug combinations are compared with the theoretical additive effect (or zero interaction) of the drug combination. Several methods exist to evaluate synergy including the Bliss independence model and Loewe additivity model, the latter using an isobolographic technique for the comparison of the dose equivalent effect of drugs when used alone compared with their combined effect. The use of dose equivalence is attractive because it requires a comparison of the dose–response relationship for two drugs (though it is possible to undertake an analysis of n combinations of drugs) at different effect levels (e.g. between 10 and 90% Emax) to calculate the zero interaction (i.e. theoretical additive response). This can be represented by a 3D response surface that can be used to compare all possible combinations of drug pairs. Furthermore, with the aid of computing this mathematical approach is amenable to analysis and to determine statistical significance. Whilst much of our understanding of drug synergy stems from in vitro studies, these mathematical approaches can be used to study drug synergy in human subjects. Indeed, a number of studies have used an isobolographic method to demonstrate synergy between various combinations of anaesthetics and of analgesics in clinical studies. A similar question as to possible synergism should be asked with the increasing move to fixed dose combinations of long acting beta agonists/ long-acting

muscarinic antagonists for the management of chronic obstructive pulmonary disease. [24, Rank 4]

## Preclinical Studies

A number of studies have investigated whether combinations of β2-agonists and muscarinic antagonists yielded synergistic bronchoprotection. For example, a synergistic interaction between tiotropium bromide and carmoterol and tiotropium bromide and olodaterol has been reported against airway obstruction in the guinea pig in vivo. In a third study, evidence was provided to support the view that combination of ipratropium bromide and salbutamol, in a dose ratio equivalent to Combivent® was synergistic. The data presented in those studies is difficult to interpret since the authors did not use a mathematical approach based on drug equivalence to specifically analyse for additivity or synergy. In two out of three of these studies, the data was re-analysed based on the information provided (see Supplementary file for interested readers) and there was some evidence for drug synergy between a β2-adrenoceptor agonist and muscarinic antagonist.

The underlying mechanism of the synergism is not well understood although evidence is emerging from studies to suggest that the long-acting muscarinic antagonist component of the combination might disinhibit GI mediated suppression of calcium activated potassium channel opening. This would lead to hyperpolarization of the airway smooth muscle membrane and hence promote relaxation induced by activation of the canonical Gs pathway. This would not only lead to further activation of these ion channels but also other intracellular signalling pathways involved in mediating relaxation by the long-acting beta agonist component. [25, Rank 2]

## Clinical Studies

A recent study has documented synergy between the bronchodilator effect of glycopyrronium bromide and indacaterol in chronic obstructive pulmonary disease patients. The bronchodilator response to an inhaled dose of glycopyrronium (50 μg) or indacaterol (150 μg) alone and in combination was monitored over 3 h. In order to determine synergy, the bronchodilator response at each time point was expressed as a percentage of the maximum bronchodilation observed with salbutamol in the same patients and then using the Bliss independence method to evaluate synergy. It appears that synergism was only observed during the rising phase of the bronchodilator

response, but not at its peak.

Numerous clinical studies have reported the beneficial effects of the combined use of long-acting beta agonists and long-acting muscarinic antagonists over a number of variables indicating benefit; these included improvement in trough FEV1, rates of exacerbation, dyspnoeic event as well as control of symptoms for tiotropium bromide/ indacaterol, umeclidinium bromide/ vilanterol, and glycopyrronium bromide/ indacaterol.

This beneficial effect, of the combination therapy versus drug component, appear to be most marked for the spirometric variables (mostly reflecting the large airways), while less evident on disease control and disease progression, a not unexpected finding in view of the fact that the drugs used are not considered disease modifiers. One would anticipate that a change in baseline FEV1 might be reflected by an increase in the diameter of the small airways resulting in lung deflation and a reduction in lung volume and consequently improvements in symptom scores and reduction in rates of exacerbation of symptoms and therefore the clinical relevance of the findings could be questioned.

To date, there are no studies that have systematically compared the bronchodilator effectiveness of long-acting beta agonist or long-acting muscarinic antagonist used alone or in combination on spirometric variables including FEF25-75, MFEF, impulse oscillometry or high-resolution computer tomography (HRCT) to monitor changes in small airway calibre. Assuming that small airway calibre is improved, the additional benefit achieved with the combination does not appear to be reflected in symptom scores. Alternatively, symptoms associated with chronic obstructive pulmonary disease may be independent of FEV1 per se and more sensitive indices that reflect residual lung volume, or use of forced oscillation techniques to monitor the calibre of small airways might show a better relationship between changes in spirometry and symptoms. Alternatively, bronchodilators can reduce airway wall stiffness which might also contribute to their ability to reduce dynamic hyperinflation and lung volume.

In theory the advantage of fixed dose combination over monotherapy would be to provide additional bronchodilation particularly if some patients are insufficiently dosed on monotherapy while combination therapy offers the opportunity of reducing the dose of each bronchodilator, but not at the expense of clinical effectiveness, while reducing the risk of adverse side effects with high dose monotherapy. Indeed, a greater degree of airway obstruction, indicative of

more severe disease, reduces bronchodilator effectiveness particularly with lower doses of bronchodilator. Hence, maintaining high levels of bronchodilator tone with combination therapy could be advantageous. [26, Rank 2]

None of the clinical trials that have demonstrated a greater degree of bronchodilation afforded by fixed combination doses over monotherapy were designed to specifically address the question of synergy. Therefore, an analysis was undertaken using the available literature to investigate whether fixed dose combinations of umeclidinium bromide/ vilanterol and glycopyrronium bromide/ indacaterol are synergistic. These studies were chosen because dose–response relationships for each of these bronchodilators have been published and large clinical trials in moderate to severe chronic obstructive pulmonary disease have been undertaken which provides an adequate and relevant data set for analysis. Moreover, there is no evidence that there is anything demonstrably unique concerning the bronchodilator effectiveness of a range of long-acting beta agonist's and long-acting muscarinic antagonist's and any difference between them could be reasonably attributed to the use of doses that were not clinically equi-effective.

Dose–response relationships for umeclidinium bromide and vilanterol were plotted using linear regression of the log dose versus trough FEV1 after 1-month treatment. These data also included the single drug data sets from the publications that compared fixed dose combination with either bronchodilator alone. It is noticeable that the slope of the dose–response relationship is flat particularly in the case of umeclidinium bromide. The dose (μg) and 95% confidence interval (95% CI) which caused a 150 mL difference in trough FEV1 was 250 (62–1010) and 55 (16–181) for umeclidinium bromide and vilanterol, respectively. A change of 160 mL in FEV1 is considered clinically important and related to a change in St George's respiratory questionnaire (SGRQ) of four units. Several studies have evaluated the effects of different fixed dose combinations of these agents (umeclidinium bromide/ vilanterol) including 125/25 μg evaluated over a 24-week period and 52-week period and 62.5/25 μg over a 24-week period. [27, Rank 3]

In all cases, there were significant improvements in the primary objective measure of trough FEV1 with combination versus single drugs and in other spirometric measures (e.g. peak FEV1); however, only the trough FEV1 data was analysed because dose–response relationships for these indices of symptoms was not available. As with earlier trials, the combination therapy is not

always demonstrably better than single drugs in terms of risk of exacerbation rate, quality of life scores and dyspnoea scores. For example, improvement in the SGRQ score was greater with the 125/25 µg dose combination compared with the single drugs, although this was not confirmed in another study in patients with similar disease severity. For a lower dose combination (62.5/25 µg), the improvement in trough FEV1 over the component bronchodilators did not translate to a significantly greater improvement in symptoms scores though in both studies, the risk of exacerbation was similar across all treatments. Using a different long acting beta agonists/ long-acting muscarinic antagonist combination, it was demonstrated that glycopyrronium bromide/ indacaterol (50/110 µg) was associated with significant improvement in trough FEV1, reduced exacerbation rates and improvement in symptom scores compared with glycopyrronium bromide alone as there was no long-acting beta agonist arm of the trial. Whether some of these studies were not powered or not of sufficient duration (e.g. maximum study period was 1 year) to detect differences in rate of exacerbation and symptom score is a distinct possibility.

The 'bronchodilator potency' of the combination was defined as the dose of bronchodilator which caused a 150 mL improvement in trough FEV1 and this was four times lower than that which could be ascribed to an additive effect. Furthermore, the interaction index (alpha) was significantly different from unity which is also indicative of synergy at both dose combinations. The latter estimate implies that a 10–20 fold reduction in the combination dose will achieve the same effector response as either drug acting alone. There was also a significant difference in the observed and the expected trough FEV1 values, again supporting the notion of synergy. [28, rank 3]

A second analysis of the bronchodilator effectiveness of fixed dose combinations of glycopyrronium bromide and indacaterol also shows evidence of synergy. Dose–response data for glycopyrronium bromide as well as single dose studies plus dose–response data for indacaterol was analysed using linear regression for trough FEV1 values versus log dose (µg). The dose (mean with 95% CI) producing a 150 mL improvement in trough FEV1 was 152 (90–258) and 320 (104–986) µg for glycopyrronium bromide and indacaterol respectively. Various studies have examined the effect of fixed dose combinations of glycopyrronium bromide and indacaterol of 50/110 µg and 50/300 µg and the

improvement in trough FEV1 by each bronchodilator alone was also used in the determination of bronchodilator potency. The 'bronchodilator potency' of the combination when defined as the dose which caused a 150 mL improvement in trough FEV1 was an order of magnitude greater than that which could be ascribed to an additive effect. Furthermore, the interaction index (alpha) was less than unity again indicative of synergy at both dose combinations tested. The analysis implies that a 10–20 fold reduction in the combination dose will achieve the same effector response as if either drug was acting alone. There was also a significant difference in the observed and expected trough FEV1 values supporting the presence of synergy.

It is important to acknowledge some limitations in the foregoing analysis. The data was obtained from a number of clinical studies with different treatment durations and whilst the subjects tended to be predominantly within the moderate to severe disease classification, one cannot rule out possible differences in bronchodilator response in different patient cohorts and differences in measurement of FEV1 between different clinical sites. The bronchodilator response to each single component in the combination clinical trials was included in the analysis to obtain better estimates of drug potency across a number of studies. However, there may have been an overestimation of the bronchodilator potency of the fixed combination and the interaction index because the dose–response relationships of each bronchodilator was characterized by low slope values and coupled with the constraint of limited number of different fixed dose combinations available for analysis. The analysis would have benefited if the fixed dose combinations had the same proportions of long-acting beta agonist/ long-acting muscarinic antagonist and if the number of fixed dose combinations was greater than that which was available for analysis so as to give better estimates of potency and the interaction index for the combination therapy. Furthermore, each bronchodilator and different combinations of the bronchodilators should be evaluated in the same patient using crossover designs, or alternatively by recruiting a relatively large patient group and using a parallel design. [29, Rank 4]

## Bifunctional Molecules

Another approach to achieving better drug therapy of chronic obstructive pulmonary disease could be in the development of dual acting muscarinic antagonism and β2-agonism (MABAs) (as shown in figure 23)

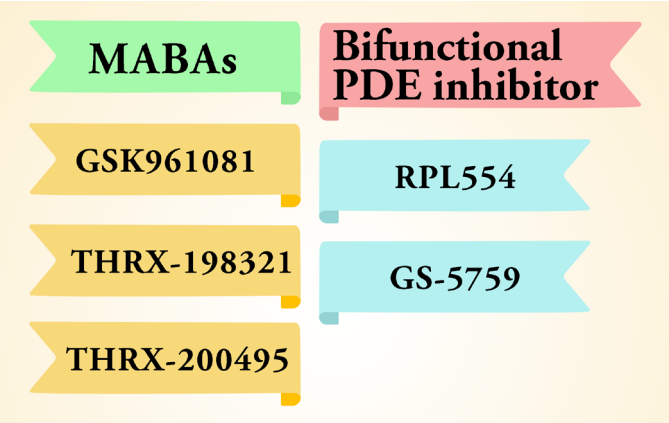


Figure 23: Examples of bifunctional molecules

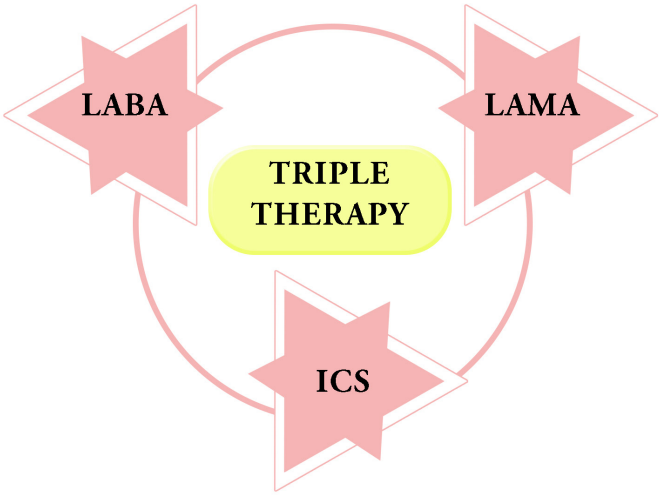


Figure 24: Triple therapy

suitable for once-a-day treatment as exemplified by GSK961081.

This drug offers the advantage of a single molecule with a single pharmacokinetic profile and potential benefits concerning formulation of one as opposed to two separate molecules which offers greater simplicity for patients undergoing triple therapy (as shown in figure 24, 25) with combination long-acting beta agonist/ long-acting muscarinic antagonist /inhaled corticosteroids in chronic obstructive pulmonary disease

It might not be unreasonable to suggest that MABA's are inherently synergistic in terms of their pharmacological effect on airway calibre. A change from baseline trough FEV1 was 215 and 277 mL with a once daily dose of 400 and 800 μg GSK961081, respectively. GSK961081 has both a β2-adrenoceptor agonist (carbostyryl group) and muscarinic antagonist (biphenyl carbamic acid) pharmacophore that are covalently linked. The pharmacological characteristics of this molecule include non-selectivity for different muscarinic receptor subtypes and selectivity for β2- versus β1-adrenoceptors. This drug class is characterized by a relatively short half-life on either receptor which cannot account for the long duration of action seen in vivo as a bronchodilator. Such a long duration is likely due to retention of the drug within the lung environment. This is reflected in a 2–3 fold order of magnitude difference in selectivity for the airways over extra-pulmonary sites containing muscarinic and β 2-adrenoceptors.

One characteristic not been reported for GSK961081, but is a feature of this drug class, is the simultaneous binding to orthosteric and allosteric sites of the muscarinic and β2-adrenoceptor. As a consequence, these molecules can retard the dissociation of an orthosteric ligand from

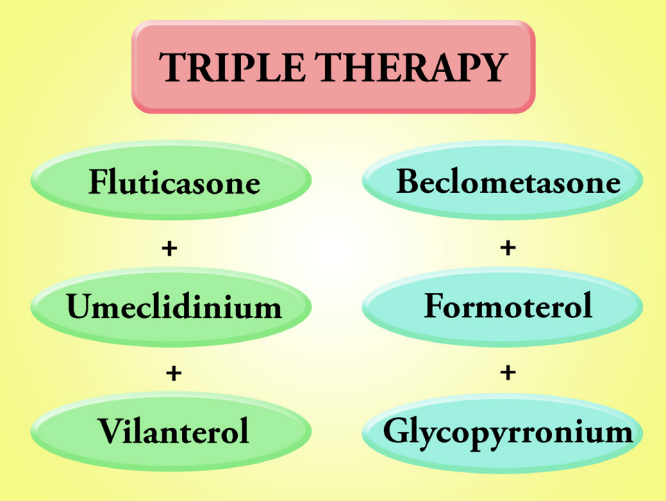


Figure 25: Examples of triple therapy

these receptors as exemplified by the prototypical muscarinic antagonism and β2-agonism, THRX-198321 which contains a nine carbon aliphatic chain between the two binding moieties. This unique property might manifest in greater clinical effectiveness because of synergistic effects as suggested for THRX-200495 which contains a propyl ethyl biphenyl ether linker group. Whilst THRX-200495 was investigated for additivity and synergy in guinea-pigs, a formal mathematical assessment of dose equivalence was not undertaken. It would appear that this agent does demonstrate synergy, but only at low to moderate dose combinations. No formal statistical analysis could be undertaken hence the estimates are qualitative in nature. Notwithstanding the fact that the selectivity of the β2-agonist and muscarinic antagonist components of the MABA was assumed to be 1:1, the analysis suggests that a three-fold lower dose of the muscarinic antagonism and β2- agonism is required to produce an equi-effective response with either component acting alone. [30, Rank 3]

## Bifunctional PDE Inhibitors

RPL554 is a mixed PDE3/4 inhibitor that has been demonstrated to have bronchodilator and bronchoprotective activity in mild asthmatic subjects and patients with chronic obstructive pulmonary disease, a feature not observed to any degree with oral or inhaled phosphodiesterase-4 inhibitors. It was previously shown that cilomilast does not cause bronchodilation per se when measured after a single oral dose and for roflumilast, the changes in baseline FEV1 in chronic obstructive pulmonary disease develops over a period of weeks.

The modest success of the phosphodiesterase-4 inhibitor roflumilast for the treatment of chronic obstructive pulmonary disease has kept interest in the PDE field for the development of new drugs for the treatment of this disease. The additional bronchodilator benefit observed in patients who were maintained on long-acting beta agonist or long-acting muscarinic antagonist is unlikely to be attributed to a direct action on airway smooth muscle, since functional studies in vitro demonstrate that roflumilast at

concentrations that are two to three orders of magnitude greater than the Ki for inhibition of phosphodiesterase-4 is without demonstrable relaxant activity. Hence, the improvement in FEV1 is likely to be due to an anti-inflammatory activity as evident by the ability of this drug class to suppress neutrophil recruitment to the airways and various inflammatory biomarkers of relevance to chronic obstructive pulmonary disease. This is also consistent with the ability of roflumilast to cause improvements in quality of life scores and reduce rates of exacerbation by virtue of an anti-inflammatory activity. Intriguingly, a number of inhaled phosphodiesterase-4 inhibitors administered daily for between 1 and 6 weeks have proved disappointing in a number of phase II clinical trials despite evidence for phosphodiesterase-4 inhibitory activity; however, this was not sufficient to result in any clinical benefit. The reason for a lack of clinical effectiveness of these highly potent and long lived inhaled phosphodiesterase-4 inhibitors might be a result of the presence of other PDE subtypes within the lung (e.g., PDE2, 3, 7) that might contribute to airway inflammation in chronic obstructive pulmonary disease. The mixed PDE3/4 inhibitor, RPL554 was evaluated in a number of phase II clinical trials in both asthma and chronic obstructive pulmonary disease subjects and shown to be an effective bronchodilator of comparable effectiveness to salbutamol and with long duration of action following single nebulized dose (circa 6–10 h). Of particular interest was the ability of this inhaled drug, administered daily for up to 1 week, to inhibit neutrophil recruitment to the airways and consequently the first demonstration of an inhaled PDE inhibitor with an anti-inflammatory signal. Furthermore, relaxation of human airways in vitro was augmented when combinations of RPL554 and atropine or glycopyrronium bromide, was used and there was evidence of synergy using the method of dose equivalence. [25, rank 5]

Another strategy has been the linking of a phosphodiesterase-4 inhibitor with a β 2-agonist (indacaterol) with a view to develop a bifunctional bronchodilator and anti-inflammatory drug. GS-5759 inhibited cytokine release, oxygen radical production and chemokine release from various inflammatory cells and it appears the β 2-agonist component of the molecule participates in the anti-inflammatory activity of the phosphodiesterase-4 component. Interestingly, this bifunctional molecule was more effective than roflumilast in some of the in vitro assays and suggests that anti-inflammatory activity can be boosted by agents which elevate cyclic AMP within target cells. Hence, bifunctional or mixed

PDE inhibitors offer the advantage of providing both a bronchodilator and anti-inflammatory activity which would be beneficial to the patient. [22, Rank 4]

## Anti-inflammatory Drugs

Like many inflammatory diseases, the complex interplay between inflammatory cells and structural cells within the lung and the mediators they release provides a wealth of potentially novel targets to treat respiratory conditions such as chronic obstructive pulmonary disease. Glucocorticosteroids are potent anti-inflammatory drugs and can reduce the rate of moderate to severe exacerbation but at the expense of the development of pneumonia and fractures and whilst combination long-acting beta agonist/ glucocorticosteroid was no better than a long-acting muscarinic antagonist in reducing the rate of exacerbation in chronic obstructive pulmonary disease, mortality was significantly lower and quality of life better with dual therapy. Withdrawal of glucocorticosteroid treatment from a triple therapy regimen did not appear to lead to a deterioration of disease but was associated with a worsening in baseline spirometry compared with placebo. Finally, glucocorticosteroids do not appear to reduce the annual rate of decline in FEV1 in chronic obstructive pulmonary disease and patients with severe chronic obstructive pulmonary disease do not appear to benefit in terms of reducing rates of exacerbation, from adding glucocorticosteroid to long-acting beta agonist compared with long acting beta agoinsts alone despite improvement in FEV1. These studies clearly highlight the unmet need to develop new types of anti- chronic obstructive pulmonary disease agents.

The documented presence of cells of the innate and adaptive immune system in chronic obstructive pulmonary disease could provide suitable targets. The proteinase hypothesis of chronic obstructive pulmonary disease also provides numerous drug targets, for example neutrophils which are implicated in the pathogenesis of chronic obstructive pulmonary disease, secrete neutrophil elastase which plays a role in stimulating mucus secretion and damage to the parenchymal tissue. Unfortunately, the neutrophil elastase inhibitor, AZD9668 was without clinical benefit in symptomatic chronic obstructive pulmonary disease patients taking tiotropium bromide following a 3 months treatment protocol. The lack of effect of this treatment on biomarkers of matrix degradation indicates that pharmacodynamic relevant concentrations were not achieved in the lung and hence the primary outcome measure was not evident. Alternatively, other proteinases (e.g.

MMP's) implicated in chronic obstructive pulmonary disease would be unaffected by this treatment. [20, Rank 4]

## Future Therapeutic Strategies

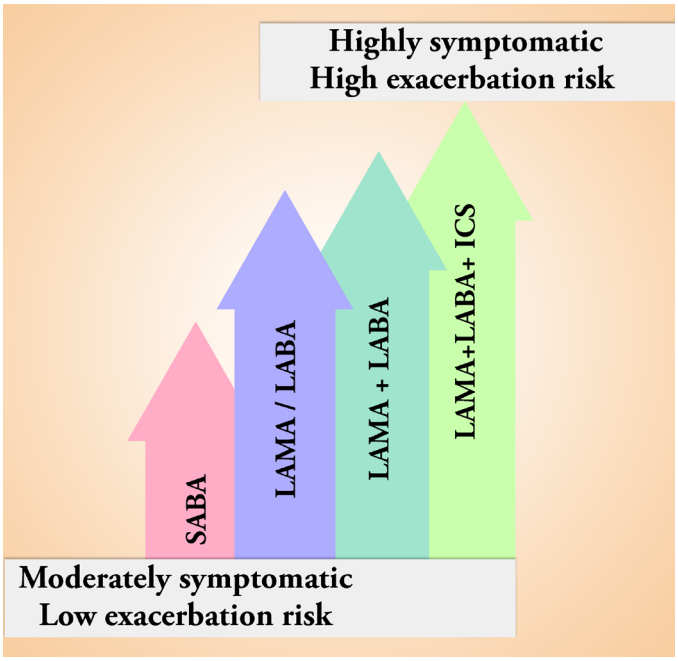


Figure 26: Pharmacological management strategies in COPD

A multiple treatment comparison meta-analysis of 26 studies has compared the effects of various combinations of treatments and noted that, although combination therapies differ in their effects for reducing the risk of chronic obstructive pulmonary disease exacerbations, they reduce risks more than monotherapy. Further studies are required to confirm the optimal combinations for reducing exacerbations (as shown in figure 26). However, randomized controlled studies to evaluate the effects of treatments on exacerbation risk are ongoing or have recently completed, such as the FLAME study comparing IND/ GLY with SFC, and a comparison of umeclidinium/ vilanterol/ fluticasone furoate with fixed-dose dual combinations of fluticasone furoate/ vilanterol and umeclidinium/ vilanterol. Various other combination therapies are being developed for the prevention of exacerbations, including triple therapies of inhaled corticosteroids/ long acting beta agonists/ long-acting muscarinic antagonist. In addition, combined phosphodiesterase-3 and phosphodiesterase-4 inhibitors (RPL554), monoclonal antibodies and p38 mitogen activated protein kinase inhibitors are in development for the prevention of exacerbations. Benralizumab, an anti-interleukin-5 (IL-5) receptor alpha monoclonal antibody, has been investigated in Phase II studies in patients with sputum eosinophilia and chronic obstructive pulmonary disease. Although no significant benefit was noted with benralizumab on the rate of exacerbations in the overall study population, a non-significant numerical improvement was seen in subgroups of patients with elevated blood eosinophils. [15, Rank 5]

## Conclusion

Although chronic obstructive pulmonary disease is specifically defined, it is a vastly heterogenous condition and the experience of living with it differs from one individual to another, both in its impact on quality of life and manifestations of the disease. There are currently several treatment options/actions (as shown in figure 27) for patients with chronic obstructive pulmonary disease that can help to reduce and/or manage their symptoms, including pharmacologic therapies, pulmonary rehabilitation, and smoking cessation, all of which can also improve bronchodilation, reduce the frequency and severity of exacerbations and improve health status and exercise tolerance. However, many patients still suffer from regular symptoms that affect their daily lives and lead to increased morbidity. Therefore, selecting the right therapies and optimizing treatment to reduce airway obstruction and improve symptoms is key in improving quality of life for each patient with chronic obstructive pulmonary disease. [10, Rank 5]

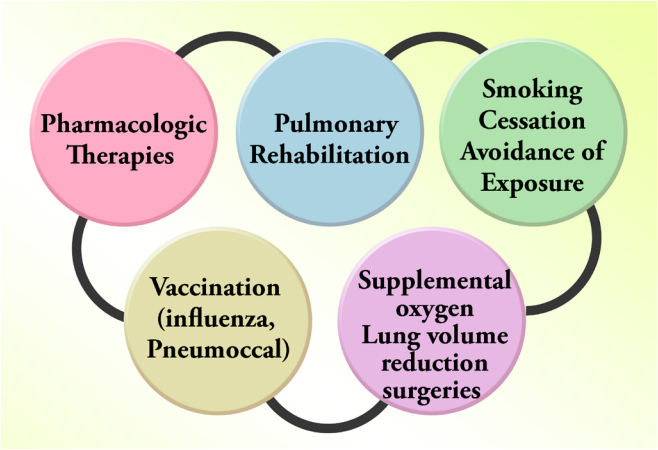


Figure 27: Therapeutic management strategies in COPD

*Important information for post-test is highlighted in red letters, boxes and diagrams.

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