

An update on chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide. It is a chronic condition which affects the respiratory system and worsens over time. Cigarette smoking and advancing age are the two major risks associated with this disease. It is concerning that the global incidence of this chronic illness is on the rise. Current projections indicate that it will become the third leading cause of death by the year 2020. Inflammatory changes underlie the pathophysiology of COPD. Irreversible damage and progressive narrowing of the air passages follow. COPD is characterised by the progressive loss of lung function. In addition, the Global Initiative for Chronic Obstructive Lung Disease released the latest update on its global strategy for the diagnosis, management, and prevention of COPD in 2015. This article provides an overview of the causative risk factors, underlying disease process, pathophysiological changes, and the classification and management of COPD, including the latest perspectives on this highly prevalent condition.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide. It is a chronic condition which affects the respiratory system and worsens over time. COPD encompasses two clinical entities, namely chronic bronchitis and pulmonary emphysema. As may be expected from a chronic illness, periods of stable COPD are interspersed with episodes of acute exacerbations, i.e. COPD relapses. COPD is largely associated with the deterioration of lung function. Typically, it presents with respiratory symptoms, such as shortness of breath and a productive cough. Chronic bronchitis is characterised by inflammation of the bronchioles, and emphysema by permanently enlarged alveolar air spaces. COPD exacerbations significantly increase the rate at which the lung function deteriorates, as well as the mortality rate associated with this disease.¹⁻³

It is predicted that COPD will become the third leading cause of global mortality by the year 2020. Currently, the COPD-associated mortality rate is increasing. It is associated with a high socio-economic burden, and has a very significant impact on the quality

of sufferers' lives. Cigarette smoking and old age are the primary drivers of COPD. The former is associated with the inhalation of pollutant particles which set pathophysiological changes in motion, ultimately resulting in damage to the lung tissue. Current treatment options are only capable of managing bronchiolar smooth muscle spasm and inflammation.^{1,3,4}

Aetiology and pathogenesis

The major risk factors involved in the causation of COPD can be divided into two groups, i.e. those that are exposure related versus those that are host related, as depicted in Table 1.⁵

COPD is mainly characterised by a sequence of pathological events which trigger inflammatory changes within the airway. Irreversible damage and progressive narrowing of the air passages follow, resulting in the impairment of smooth air flow through the lower respiratory tract. The major pathophysiological mechanisms that underlie the development of COPD are illustrated in Figure 1.^{6,7}

Exposure to a variety of air pollutants collectively contributes to COPD, with cigarette smoking being the major causative factor.

Table 1: Risk factors associated with the development of chronic obstructive pulmonary disease⁵

Major risk factors involved in the causation of COPD

Exposure related	Host related
<ul style="list-style-type: none"> • Environmental tobacco smoke • Occupational dust and chemicals • Environmental pollution, including air pollution 	<ul style="list-style-type: none"> • Airway hyper-responsiveness • Genetic predisposition (AAT deficiency) • Impaired lung growth

AAT: alpha-1 antitrypsin, COPD: chronic obstructive pulmonary disease

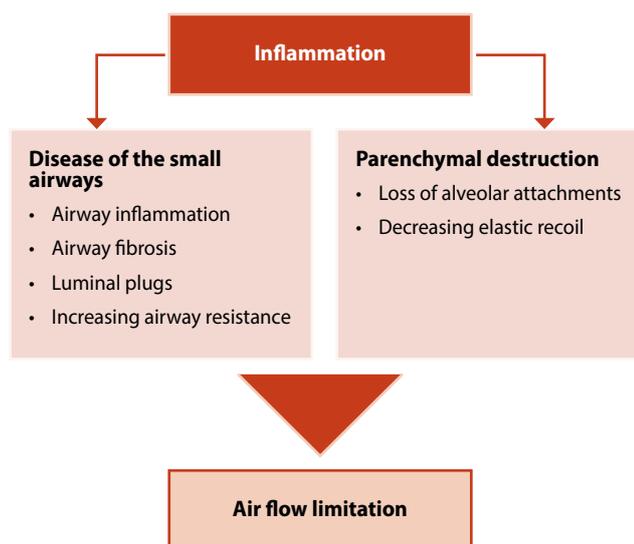


Figure 1: Mechanisms involved in the development of chronic obstructive pulmonary disease⁶

By description, there is a gradual loss of the alveolar surfaces in the lungs, also clinically referred to as emphysema; and the production of mucus accompanied by an inflammatory response to the damage which is caused to the cells of the lung surfaces, defined as chronic bronchitis. The impact of a genetic mutation is another causative factor that is attributed to the development of COPD. However, this is only applicable to a small portion of the patient population.^{6,8}

Alpha-1 antitrypsin (AAT) is synthesised and secreted in two major body organs, i.e. the lungs and the liver, as well as in certain types of white blood cells, with the liver being the major site of its synthesis. AAT plays a vital role in inhibition of the activity of the enzyme, neutrophil elastase, which has destructive properties which are meant to form part of normal white blood cell defence mechanisms against invading pathogens. The neutrophil elastase has the potential to overreact and damage normal body cells, which, in the case of COPD, may be the lung tissue itself.

Hence, there is a need for AAT to control and limit this enzyme's rate of activity, thereby avoiding "self-cell destruction" of the

lungs. The Z-variant of AAT is an ineffective protein that may arise as a consequence of a genetic point mutation, which results in a decrease in normal AAT secretion, a greatly reduced ability to inhibit neutrophil elastase, and accumulation within the epithelial cells of the bronchioles. This, in turn, promotes a pathogenic process within the lung parenchyma, and could contribute to the causation of pulmonary emphysema and chronic bronchitis.⁹

Cigarettes contain more than 6 000 different molecular entities and multiple toxins that are released into the lungs to initiate an inflammatory response. Smoke interacts with the lung macrophages, as well as the epithelial cells lining the airways and the alveoli, thus influencing the release of chemokines which mediate the inflammatory response. Smoke has the potential to cause the activation of humoral inflammation, a process which sequentially leads to the production of C5a, a potent chemotactic agent, which has its effect enhanced by a co-factor, Gc-globulin. In addition to inflammation, lung tissue damage involves a variety of multifaceted interactions, such as extracellular matrix proteolysis, apoptosis and autophagic cell death, which result in loss of the elastic properties of the lungs, as well as loss of the intact structures which maintain the normal shape, therefore leading to shrinkage.^{10,11}

Clinical presentation

A diagnosis of COPD is made based on the patient's signs and symptoms, and lung function tests. These indicators are used jointly to increase the likelihood of correctly diagnosing the patient with COPD. The likelihood of COPD increases in patients aged ≥ 40 years. Once specific factors have been identified, spirometry is used to establish a diagnosis of COPD.⁶ The key indicators are described in Table 2.

According to the latest guidelines, *Global strategy for diagnosis, management, and prevention of COPD – 2016*, of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the use of screening spirometry is no longer advised. Spirometry should only be used after basic screening of high-risk patients has been performed. Spirometry in the post-bronchodilator setting, as a means of identifying air flow limitation, remains at a level of forced

Table II: Indicators that may lead to a diagnosis of chronic obstructive pulmonary disease⁶

Indicator	Description	Checklist
Dyspnoea	That worsens over time, i.e. is progressive	✓
	That worsens with exercise or exertion	✓
	That is persistent	✓
A chronic cough	That may be intermittent and unproductive	✓
Chronic sputum production	Chronic sputum production	✓
Risk factor exposure	Tobacco smoke (in any form)	✓
	Smoke from cooking at home and from heating fuels	✓
	Occupational dust and chemicals	✓
A family history of COPD	A family history of COPD	✓

COPD: chronic obstructive pulmonary disease

expiratory volume in one second (FEV₁)/forced vital capacity (FVC) of ≤ 0.7 , and can be used to confirm the diagnosis of COPD. A short-acting β_2 agonist, at a dosage of 400 μg , and/or an anticholinergic (passive bronchodilator) at 160 μg , can be administered, and the FEV₁ should then be measured. The measurement of the FEV₁ can be taken 10–15 minutes after the short acting β_2 agonist, or 30–45 minutes following the administration of the short-acting anticholinergic, or when a combination of the two has been administered. Subsequently, the results are then interpreted by taking into consideration the patient's age, height, sex and race.⁶

Categorisation

To ensure that a proper diagnosis is made, and with the aim of avoiding errors in the long term, it is recommended that a spirometry assessment is used once high-risk patients have been identified. This assists in evaluating the rate and extent of limitation in air flow in each individual patient. The following should be considered as part of the assessment:^{6,12-16}

- *An evaluation of lung function, with the use of spirometry, to establish the FEV₁:* Obstruction of the air flow is a primary parameter, used widely to measure the extent of exacerbation, or the presence of COPD in the first place. Resistance to pulmonary air flow is observed when the ratio of FEV in one second to the FVC is reduced.
- *Respiratory symptoms:* Respiratory symptoms, such as dyspnoea, coughing and shortness of breath.
- *The exacerbation history of the patient:* The exacerbation history of the patient is required to establish the level of progression from the initial time of onset or diagnosis of the disease.
- *Co-morbidity indices:* Co-morbidity indices are needed to establish the presence, and relate the effect, of any underlying conditions and disease in a given patient.

Body mass index (BMI) should be considered in the diagnosis as patients with a low BMI have a greater risk of COPD exacerbation and mortality, when compared with obese patients. Co-morbid conditions, such as diabetes mellitus and hypertension, also place patients at a higher risk of COPD exacerbations.¹⁴

Following the GOLD recommendations to include symptoms and exacerbations in the diagnostic criteria, when classifying the disease severity from A–D (Table 3), the assessment of symptoms must be performed in accordance with the COPD Assessment Test (CAT) or the modified Medical Research Council (MRC) dyspnoea scale.^{6,12}

Guidelines for interpreting the results of these assessments indicate that if the COPD assessment test score is ≥ 10 , or if the modified MRC dyspnoea scale value is ≥ 2 , then there is a high likelihood of symptoms worsening in patients in risk groups B and D. Exacerbation is assessed based on the number exacerbations experienced by the patient in the past year, or with the use of the spirometry. The degree of air flow resistance is determined with the use of severity grades ranging from 1–4. The guidelines indicate that patients classified with a severity grade of 3–4, and those who

have experienced exacerbations for the past two years, fall into risk groups C or D. However, with all of these developments, there is some doubt whether the modified MRC dyspnoea scale value of ≥ 2 sufficiently correlates with the CAT value of ≥ 10 . Hence, the approach may not be a very reliable one.¹² The management of COPD patients is based on a combined COPD assessment, which incorporates both the CAT score and the modified MRC dyspnoea scale value, and provides for the four categories (A–D) depicted in Table 3.⁶

Management

The management of COPD involves setting treatment goals based on the pathophysiology of the disease, and focuses on reducing the symptoms, as well as the overall risk, as depicted in Table 4.

Nonpharmacological

Smoking cessation is the intervention with the greatest capacity to alter progression of the disease. Smoking cessation can be

Table III: The combined chronic obstructive pulmonary disease assessment⁶

Assessing COPD	
Group A	
<ul style="list-style-type: none"> • Low risk, and fewer symptoms • GOLD 1 or 2 (mild or moderate air flow limitation) • And/or 0–1 exacerbations per year, with no hospitalisation for exacerbation • And a CAT score ≤ 10, or modified MRC dyspnoea scale value of 0–1 	
Group B	
<ul style="list-style-type: none"> • Low risk, and more symptoms • GOLD 1 or 2 (mild or moderate air flow limitation) • And/or 0–1 exacerbations per year, with no hospitalisation for exacerbations • And a CAT score ≥ 10, or a modified MRC dyspnoea scale value of ≥ 2 	
Group C	
<ul style="list-style-type: none"> • High risk, and fewer symptoms • GOLD 3 or 4 (severe or very severe air flow limitation) • And/or ≥ 2 exacerbations per year, or ≥ 1 hospitalisation for exacerbations • And a CAT score ≤ 10, or a modified MRC dyspnoea scale value of 0–1 	
Group D	
<ul style="list-style-type: none"> • High risk, and more symptoms • GOLD 3 or 4 (severe or very severe air flow limitation) • And/or ≥ 2 exacerbations per year, or ≥ 1 hospitalisation for exacerbations • And a CAT score ≥ 10, or a modified MRC dyspnoea scale value of ≥ 2 	

CAT: COPD Assessment Test, COPD: chronic obstructive pulmonary disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease, MRC: Medical Research Council

Table IV: Treatment goals for chronic obstructive pulmonary disease⁶

Reducing the symptoms	Reducing the risk
<ul style="list-style-type: none"> • Improving exercise tolerance • Improving health status • Relieving the symptoms with minimal side-effects 	<ul style="list-style-type: none"> • Reducing the mortality rate • Prevent and treating exacerbations • Preventing disease progression

encouraged using the 5 As model. The 5 As model assists in identifying patients who are ready to quit and in giving them advice on tobacco use:

- *Ask*: Tobacco users visiting the healthcare facility are systematically identified in this way. Enquiries should be made in a friendly, non-accusing way, and tobacco use indicated on the medical notes.
- *Advise*: Advice should be tailored to each specific patient, should be clear and strong, and must have the aim of persuading the patient to quit.
- *Assess*: This is a measure of the willingness of the patient to make an attempt to quit.
- *Assist*: This refers to the action of the healthcare worker with regard to supporting the patient via a specific plan to quit, and providing support and recommendations on the suitable use of medication.
- *Arrange*: This refers to the planning of follow-up visits or contact with the patient, either in person or by telephone.^{6,17}

Conversely, the 5 Rs model can be used as a guideline on motivational intervention to assist patients who are not yet ready to quit:

- *Relevance*: This is used to point out to the patient how quitting would be personally relevant to him or her.
- *Risks*: It is important to encourage the patient to identify the potential negative consequences of tobacco use that are relevant to him or her. These risks may include cardiovascular threats, like myocardial infarction and a stroke, and other illnesses, such as lung cancer and COPD, but also the threat to wealth or the ensuing financial burden.
- *Rewards*: This refers to making the patient aware of the potential benefits of stopping using tobacco, for example, the resultant improved health, an improved sense of smell and taste, saving money, and general improvement in his or her feeling of well-being.
- *Roadblocks*: It is important to identify any barriers to quitting tobacco products, and to provide advice on treatment options to address these barriers, i.e. withdrawal symptoms, weight gain, depression and association with other tobacco users.
- *Repetition*: Repetition is indicated if the patient is still not ready to quit, in which case he or she should be re-assessed at a later stage with regard to his or her readiness to do so, and the intervention repeated then.¹⁷

Identifying patients who are ready to quit smoking, and providing motivational measures to assist patients to quit smoking, should be every healthcare provider's responsibility. Motivational interviewing is an evidence-based approach to helping patients to change their habits concerning tobacco use. However, counselling and medication have both been shown to be effective in treating tobacco dependence, but using medication together with counselling has been shown to be more effective than using either one alone.^{18,19}

Older patients and/or patients with severe COPD should be offered a pneumococcal and influenza vaccine. Vaccination can

prevent some of the infections responsible for severe COPD exacerbations.^{5,6}

Pharmacological

A distinction should be made between the stable form of the disease, and the management of exacerbations, when managing COPD pharmacologically. Pharmacotherapy should aim to:⁶

- Achieve a reduction in the severity of the symptoms
- Reduce the frequency and severity of exacerbations
- Improve the overall health status and the patient's ability to tolerate physical activities and exercise

However, current treatment options cannot definitively modify the characteristic reduction in pulmonary function seen in patients suffering from this disease. The current mainstay of COPD treatment consists of two important classes of pharmacotherapeutic agents, i.e. bronchodilators (active and passive) and glucocorticosteroids.⁶

Bronchodilators

Bronchodilators cause relaxation of the bronchial smooth muscle, and therefore facilitate bronchodilatation. The bronchial smooth muscle contains both muscarinic and β_2 -adrenergic receptors. This provides two possible mechanisms of drug action, i.e. active and passive bronchodilatation.^{3,20}

Selective β_2 -receptor agonists

These drugs are selective agonists at the β_2 -adrenergic receptors (also referred to as the β_2 adrenoceptors) of the bronchial smooth muscle when they are inhaled directly into their biophase (i.e. when a localised effect is achieved on the smooth muscle of the lower respiratory tract). When administered intravenously, or even orally, they lose their selectivity and produce cardiac (β_1 -receptor) and other systemic effects as well. Examples of short-acting agents are salbutamol (also known as albuterol), fenoterol, levalbuterol, hexoprenaline (no longer available) and terbutaline. By increasing the concentration of cyclic adenosine monophosphate (cAMP), these drugs act as active bronchodilators. Therefore, they achieve the functional antagonism of bronchoconstriction. Patients should be monitored for side-effects such as tachycardia, palpitations, cardiac dysrhythmias, anxiousness, dizziness and skeletal muscle tremors.^{3,6,20}

In contrast to the short-acting β_2 agonists (SABAs), which have an average onset of action of approximately half an hour or less, and a duration of action in the range of 4–6 hours; long-acting β_2 agonists (LABAs) have a slower onset and more sustained duration of action, lasting up to 12 hours. Examples of the latter are salmeterol, formoterol, arformoterol and indacaterol, as well as vilanterol and olodaterol.^{3,6,20}

Methylxanthines

Theophylline is a systemic bronchodilator with a narrow therapeutic index. Therefore, therapeutic drug monitoring is

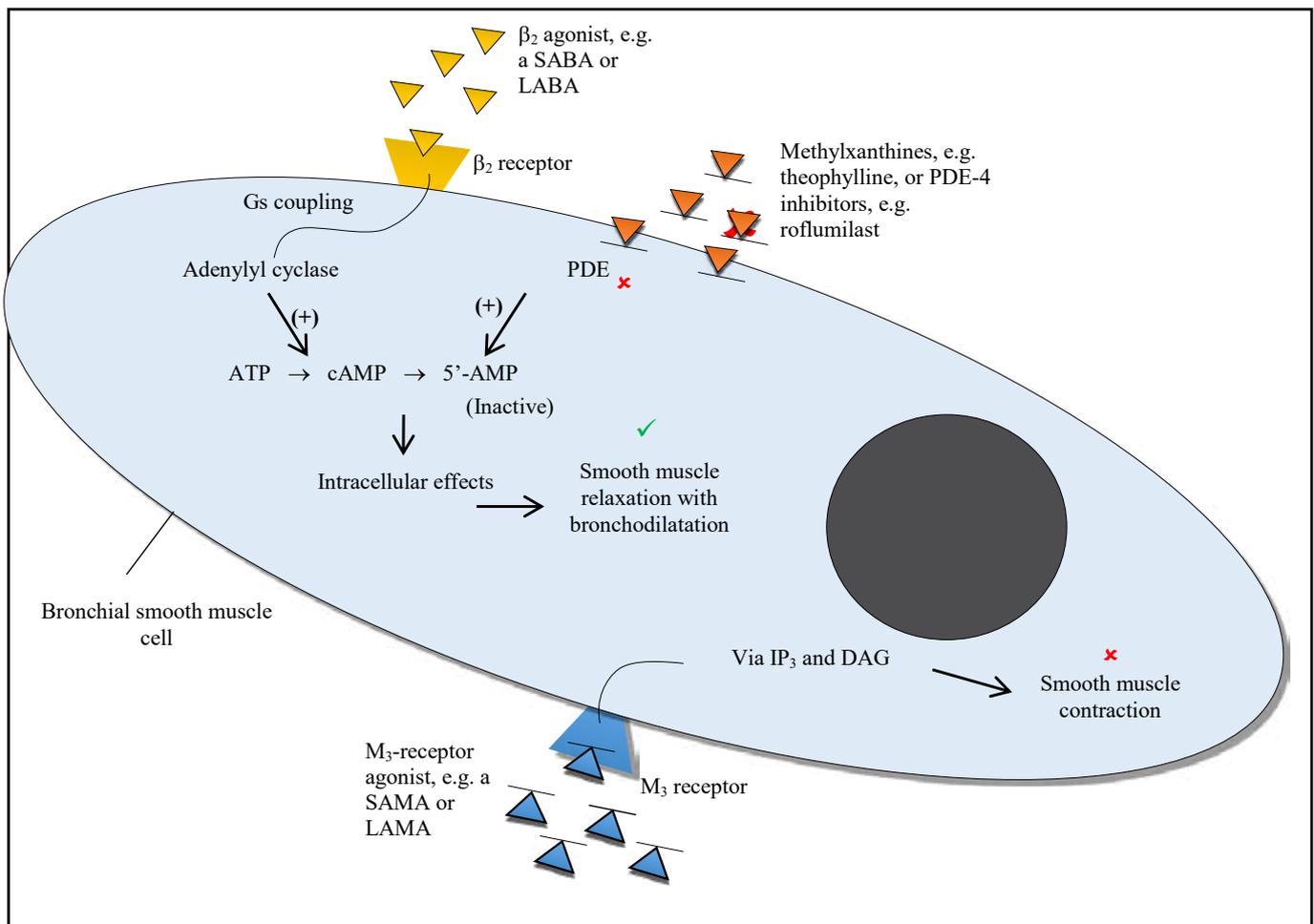


Figure 2: The mechanism of action of the different classes of bronchodilators*

*: β_2 -receptor stimulation produces stimulatory G-protein coupling, which results in the activation of adenylyl cyclase, that, in turn, converts intracellular adenosine triphosphate to cyclic adenosine monophosphate, the second messenger that produces bronchial smooth muscle relaxation. Conversely, stimulation of the M_3 receptors results in bronchial smooth muscle contraction. (Therefore, the short- and long-acting antimuscarinic agents act as receptor blockers, thereby achieving passive bronchodilatation). On the other hand, the methylxanthines and phosphodiesterase-4 inhibitors prevent the degradation of cyclic adenosine monophosphate to its inactive form, 5'-adenosine monophosphate, through inhibition of the enzyme, phosphodiesterase. This also facilitates bronchodilatation via an increase in the concentration of cyclic adenosine monophosphate²⁰

required. It differs from the previously mentioned drugs in that it inhibits the enzyme, phosphodiesterase (PDE). This produces nonselective β -receptor effects through an increase in the cAMP concentration. It is a second-line drug. Caffeine is a methylxanthine as well. Aminophylline (theophylline-ethylenediamine) is more water soluble and may be administered intravenously. In addition to their systemic β -adrenergic effects, the methylxanthines also have a stimulatory effect on the central nervous system, resulting in increased levels of alertness, irritability, anxiousness and insomnia, with additional side-effects such as tremors, tachycardia, palpitations and cardiac dysrhythmias, as well as gastric irritation.^{3,6,20}

Roflumilast

Roflumilast is a possible treatment option in certain patients with COPD, and is a PDE-4 inhibitor, as opposed to the methylxanthines, which are non-specific PDE inhibitors, and therefore have the ability to increase the concentrations of both cAMP and cyclic guanosine monophosphate. Both roflumilast and its major active metabolite, roflumilast *N*-oxide, are potent, selective inhibitors

of PDE-4, giving rise to increased intracellular levels of cAMP. PDE-4 is present in the bronchial smooth muscle cells, as well as the immune system and proinflammatory cells, where its inhibition (and the subsequent rise in cAMP concentration) leads to the suppression of a wide variety of proinflammatory responses. Therefore, this drug can be regarded as a novel anti-inflammatory agent, rather than just a bronchodilator.^{3,6}

Antimuscarinic (anticholinergic) drugs

The short-acting drug of choice is ipratropium bromide, since it does not cause thickening of the bronchial secretions. Blocking the muscarinic receptors inhibits acetylcholine-induced bronchoconstriction, and implies that the adrenergic stimulation of β_2 adrenoceptors in the bronchial smooth muscle will not be opposed by a parasympathetic outflow from the vagus nerves. This results in bronchodilatation. Therefore, ipratropium bromide is a passive bronchodilator. [Oxipropium bromide is another example of a short-acting muscarinic antagonist (SAMA)]. Tiotropium bromide is a long-acting muscarinic antagonist (LAMA). Other examples of LAMAs are acclidinium bromide, glycopyrronium

bromide (*syn.* glycopyrrolate) and umeclidinium bromide. These drugs are of particular importance in the management of COPD. They cause very few systemic side-effects as they are poorly absorbed following inhalation.^{3,6,20}

Enhanced bronchodilatation may be achieved when combining ipratropium bromide with a SABA, such as salbutamol or fenoterol, or a long-acting selective β_2 agonist (LABA)/LAMA combination for inhalation, for example, owing to the synergism between their mechanisms of action. Several other fixed-dose combinations are available, including examples such as salbutamol/ipratropium, formoterol/acclidinium, vilanterol/umeclidinium and indacaterol/glycopyrrolate.^{3,6,20}

According to GOLD, bronchodilator therapy is central to the management of COPD symptoms, and inhalant therapy is preferred over the systemic administration of such agents. They may be prescribed, either for regular use or on an as-needed basis to manage symptoms. The LABAs and LAMAs are better at achieving sustained symptom relief than the SABAs and SAMAs. Increased efficacy can be achieved through combination therapy with bronchodilators from different classes, rather than increasing the dosage of a single agent. Roflumilast is recommended to reduce COPD exacerbations in patients with a FEV₁ of less than 50% of the predicted value, together with chronic bronchitis and regular episodes of COPD exacerbations.⁶

The major mechanisms of action of the various classes of bronchodilators are depicted and summarised in Figure 2.

The “disease modifiers”

The inhaled glucocorticosteroids, such as budesonide, beclomethasone and fluticasone, are much safer for long-term use than systemic corticosteroids. They alter the course of the disease process and are lifesaving in the long run. However, they do not manage acute bronchospasm, but decrease bronchial hyperreactivity and the risk of a relapse. Inhaled glucocorticosteroids may give rise to oral thrush, i.e. oral candidiasis. Therefore, patients are encouraged to rinse their mouths with clean water following the use of steroid inhalers. Systemic agents include prednisone and methylprednisolone.^{3,6,20}

According to GOLD, long-term therapy with the inhaled corticosteroids, in addition to long-acting bronchodilators, is recommended in patients with an increased risk of developing COPD exacerbations. Long-term steroid monotherapy is not recommended.⁶

Exacerbations

GOLD defines a COPD exacerbation as “an acute event characterised by a worsening of the patient’s respiratory symptoms beyond normal day-to-day variations, and leads to a change in medication”. The most common trigger factors are viral infections of the upper respiratory tract and tracheobronchial infections. Recommendations for the management of a COPD exacerbation include:⁶

- The use of SABAs, with or without concomitant SAMAs.
- Systemic corticosteroids and antibiotics, if indicated. These agents can achieve positive outcomes in terms of improving the FEV₁, partial pressure of oxygen in arterial blood, length of hospital stay and time to recovery from the relapse.

GOLD also mentions the following ways of reducing the number of COPD exacerbations and hospitalisation:⁶

- Smoking cessation
- Vaccination with pneumococcal and seasonal influenza vaccines
- Adequate patient education on their treatment and the correct use of inhalers
- Treatment with long-acting bronchodilators, with or without inhaled corticosteroids
- Treatment with a PDE-4 inhibitor, e.g. roflumilast

Conclusion

An accurate and timely diagnosis is required for the effective management of COPD, together with the removal of preventable risk factors (smoking cessation is the most notable), and the commencement of effective pharmacotherapeutical measures to manage the symptoms and reduce the frequency and severity of exacerbations, as well as improve the overall quality of life of these patients. However, current treatment options cannot definitively modify the characteristic reduction in pulmonary function seen in patients suffering from this disease. Active and passive bronchodilators and the glucocorticosteroids remain the backbone of the current approach to the management of COPD. Healthcare professionals need to have a thorough understanding of the disease, its categorisation, and how the different classes of bronchodilators and glucocorticosteroids feature within the current treatment guidelines for COPD. In addition, the significance of a COPD exacerbation should be clearly understood, and the need for more intensive therapy recognised. The health burden of COPD is increasing, and this disease will require a more definitive management approach in the future.

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