International Journal of Pharmaceutical Science and Research
ISSN: 2455-4685, Impact Factor: RJIF 5.28
www.pharmacyjournal.net
Volume 1; Issue 7; November 2016; Page No. 01-05

Chronic obstructive pulmonary disease: A review

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Abstract
Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, and through under-diagnosis, is often inappropriately treated. This multicomponent disease involves both airway and systemic inflammation at all stages and may influence the progression of disease and the pathophysiology of comorbidities. COPD is an umbrella term that covers many clinical subtypes with clearly different pulmonary and extra-pulmonary characteristics, but with persistent airflow limitation in common. This insight has led to the development of a more personalized approach in bronchodilator therapy, prevention of exacerbations, and advanced treatments (such as non-invasive ventilation and lung volume reduction techniques). However, systemic manifestations and comorbidities of COPD also contribute to different clinical phenotypes and warrant an individualized approach as part of integrated disease management. Over the past 15 years there has been a surge of bench and translational research regarding the genetics and pathogenesis of COPD, and several large-scale clinical trials have introduced new treatment paradigms for the condition. In this review, we have provided a deep insight of the condition with its management plan.

Keywords: Chronic obstructive pulmonary disease (COPD), non-invasive ventilation, lung volume reduction techniques

Introduction
According to National Institute of Health, COPD or chronic obstructive pulmonary disease, is a progressive disease that makes it hard to breathe. "Progressive" means the disease gets worse over time [1]. American Lung Association defines Chronic obstructive pulmonary disease (COPD), as a chronic lung disease that makes it hard to breathe which includes chronic bronchitis and emphysema [2]. According to British Lung Foundation, COPD stands for chronic obstructive pulmonary disease which describes a group of lung conditions that make it difficult to empty air out of the lungs because airways have been narrowed. This is the name used to describe a number of conditions including emphysema and chronic bronchitis [3].

Very often chronic obstructive pulmonary disease (COPD) is defined as a progressive disease characterized by increasing airflow limitation and respiratory symptoms, often associated with chronic comorbidities, leading to a significant burden for the patient[4,5].

Specific pharmacological therapy for COPD helps to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and improve exercise tolerance [4-6]. Inhaled bronchodilators, such as β2-agonists and muscarinic antagonists, improve lung function by altering airway smooth muscle tone but also act on peripheral airways [7]. They reduce air trapping and improve emptying of the lungs, thereby reducing lung volumes, improving symptoms such as breathlessness and increasing exercise capacity [4, 8].

Recently, chronic obstructive pulmonary disease (COPD) has gained interest as a major public health concern. It is currently the focus of intense research because of its persistently increasing prevalence, mortality, and disease burden. COPD was responsible for more than 2.5 million deaths worldwide in 2000 alone [9]. COPD is projected to have the fifth leading burden of disease worldwide by the year 2020 [10].

It is a condition where the airways become inflamed and the air sacs in your lungs are damaged. This causes your airways to become narrower, which makes it harder to breathe in and out. Therefore, people with COPD have breathing difficulties, and this can affect many aspects of your day-to-day life. COPD is a major cause of disability, and it's the third leading cause of death in the United States. Currently, millions of people are diagnosed with COPD. Most of the time, COPD is diagnosed in middle-aged or older adults. The disease isn't passed from person to person. COPD has no cure yet, and doctors don't know how to reverse the damage to the airways and lungs. However, treatments and lifestyle changes can help you feel better, stay more active, and slow the progress of the disease. The disease is increasingly common, affecting millions of Americans, and is the third leading cause of death in the U.S [11].

Epidemiology of Copd [12]
- Globally, ~10% of people older than 40 have airflow limitation of GOLD stage 2 or worse (FEV1 < 80% predicted); up to 25% may have GOLD stage 1 (FEV1 ≥ 80% predicted but FEV1/FVC < 0.7).
- Up to 60-85% of people with COPD (mostly mild/moderate severity) are undiagnosed.
- Besides tobacco smoking, biomass exposure (wood burning stoves), secondhand smoke, air pollution and work exposures to fumes and dusts cause COPD in susceptible people.
- COPD is the 4th leading cause of death worldwide; its mortality is rising, while cardiovascular disease's is falling; COPD is expected to be the 3rd leading cause of death in the next 20 years.

Pathophysiology [13, 20]
The term "COPD" includes two main conditions—Emphysemaand Chronic Bronchitis. In emphysema, the walls

between many of the air sacs are damaged. As a result, the air sacs lose their shape and become floppy. This damage also can destroy the walls of the air sacs, leading to fewer and larger air sacs instead of many tiny ones. If this happens, the amount of gas exchange in the lungs is reduced. In chronic bronchitis, the lining of the airways is constantly irritated and inflamed. This causes the lining to thicken. Lots of thick mucus forms in the airways, making it hard to breathe. Most people who have COPD have both emphysema and chronic bronchitis. Thus, the general term "COPD" is more accurate.

The main cause of COPD in developed countries is tobacco smoking. In the developing world, COPD often occurs in people exposed to fumes from burning fuel for cooking and heating in poorly ventilated homes.

Only about 20 to 30 percent of chronic smokers may develop clinically apparent COPD, although many smokers with long smoking histories may develop reduced lung function. Some smokers develop less common lung conditions. They may be misdiagnosed as having COPD until a more thorough evaluation is performed.

COPD symptoms often don't appear until significant lung damage has occurred, and they usually worsen over time, particularly if smoking exposure continues. For chronic bronchitis, the main symptom is a daily cough and mucus (sputum) production at least three months a year for two consecutive years.

Other signs and symptoms of COPD may include:

- Shortness of breath, especially during physical activities
- Wheezing
- Chest tightness
- Having to clear your throat first thing in the morning, due to excess mucus in your lungs
- A chronic cough that may produce mucus (sputum) that may be clear, white, yellow or greenish
- Blueness of the lips or fingernail beds (cyanosis)
- Frequent respiratory infections
- Lack of energy
- Unintended weight loss (in later stages)
- Swelling in ankles, feet or legs

People with COPD are also likely to experience episodes called exacerbations, during which their symptoms become worse than usual day-to-day variation and persist for at least several days.

Classification

The classification of COPD is according to post-bronchodilator FEV1. Post-bronchodilator FEV1 often causes confusion.It means that if patients are using short-acting bronchodilators, the measurement is taken 15 minutes after the administration of 400 microgram salbutamol.

If patients are using long-acting bronchodilators (long-acting beta-agonists or long-acting antimuscarinic antagonists), they are encouraged to take them as prescribed in the morning, and do not need extra bronchodilation before their spirometry [21].

Table 1: Severity grading of COPD according to NICE 2014 [22]

Stage	FEV_1/FVC	Post-bronchodilator FEV_1
Mild	<0.7	>80%
Moderate	<0.7	50–80%
Severe	<0.7	30–50%
Very severe	<0.7	<30%

Management

An effective COPD management plan includes four components: (1) assess and monitor disease; (2) reduce risk factors; (3) manage stable COPD; (4) manage exacerbations.

The goals of effective COPD management are to:

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

Reduction of therapy once symptom control has been achieved is not normally possible in COPD. Further deterioration of lung function usually requires the progressive introduction of more treatments, both pharmacological and nonpharmacological, to attempt to limit the impact of these changes. Acute exacerbations of signs and symptoms, a hallmark of COPD, impair patients' quality of life and decrease their health status. Appropriate treatment and measures to prevent further exacerbations should be implemented as quickly as possible [23, 25]. The Global initiative for chronic Obstructive Lung Disease (GOLD) strategy document recommends that the pharmacological therapy of chronic obstructive pulmonary disease (COPD) should be predicated according to the individual patient's level of symptoms, airflow limitation, and history of exacerbations [4]. The preferred option for maintenance therapy of COPD is long-acting bronchodilators, [4, 5] either alone or in combination with an inhaled corticosteroid (ICS).

The GOLD strategy document [4] recommends treatment with at least one long acting bronchodilator for patients with moderate-to-very severe COPD. The strategy of combining short-acting bronchodilators with different mechanisms of action, i.e., ipratropium bromide and salbutamol, has previously been shown to provide better symptomatic relief and to be cost-saving in patients with COPD [6, 7]. In line with this, more recent studies have shown that also combining long-acting bronchodilators with different mechanisms of action provides additional benefits over the use of a single long-acting bronchodilator, without significantly increasing the risk of adverse effects [26]. Previous studies have shown that combining a long-acting β2-agonist with a long-acting anti-muscarinic antagonist leads to significant improvements in symptoms and lung function compared with either type of bronchodilator used alone[8,26]. Acute exacerbations of COPD are associated with a poor prognosis in regard to health status, physical activity, decline in lung function, and mortality [27, 32]. Prevention of exacerbations is therefore of outmost importance in the management of COPD [4] and, in keeping with this, a key objective for new drugs for COPD.

The GOLD guideline treatment table is the most well-known and accepted guideline for the treatment of COPD. It can be summarized as follows:

Table 2: GOLD guidelines for management of COPD [4]

Stage: *	1 (mild)	2 (moderate)	3 (severe)	4 (very severe)
FEV1/FVC	<0.70	<0.70	<0.70	<0.70
FEV1	>= 80% pred.	50-80% pred.	30-50% pred.	<30% pred., or <50% pred. w/chronic respiratory failure
Treatment	Short-acting bronchodilator as needed for all patients with COPD.			
		Consider pulmonary rehabilitation.	Consider pulmonary rehabilitation.	Consider pulmonary rehabilitation.
		One or more long-acting bronchodilators.	One or more long-acting bronchodilators.	One or more long-acting bronchodilators.
			Inhaled corticosteroid, if repeated exacerbations.	Inhaled corticosteroid, if repeated exacerbations.
				Long-term oxygen if needed; consider lung volume reduction surgery

*All patients should receive smoking cessation counseling and influenza vaccination.
FEV: forced expiratory volume
FVC: forced vital capacity

Bronchodilators

Bronchodilators are the backbone of any COPD treatment regimen. They work by dilating airways, thereby decreasing airflow resistance. This increases airflow and decreases dynamic hyperinflation. Lack of response in pulmonary function testing should not preclude their use. These drugs provide symptomatic relief but do not alter disease progression or decrease mortality. There are three classes of bronchodilators:

- Beta-2-agonists (short-acting and long-acting)
- Anticholinergics (short-acting and long-acting)
- Methylxanthines

Generally, long-acting bronchodilators are more beneficial than short-acting ones.

Phosphodiesterase-4 (PDE4) inhibitors are taken every day to help prevent COPD exacerbations. The only PDE4 inhibitor available is roflumilast [33, 34].

Beta2-agonist bronchodilators activate specific B2-adrenergic receptors on the surface of smooth muscle cells, which increases intracellular cyclic adenosine monophosphate (cAMP) and smooth muscle relaxation [35, 36].

Anticholinergic drugs compete with acetylcholine for postganglionic muscarinic receptors, thereby inhibiting cholinergically mediated bronchomotor tone, resulting in bronchodilation. They block vagally mediated reflex arcs that cause bronchoconstriction. Clinical benefit is gained through a decrease in exercise-induced dynamic hyperinflation. These agents are poorly absorbed systemically and are relatively safe. Reported adverse effects include dry mouth, dry eyes, metallic taste, and prostatic symptoms [37, 39].

Economic Burden

Chronic obstructive pulmonary disease (COPD) is the third most common cause of death in the USA. In 2010, the cost of COPD in the USA was projected to be approximately US$50 billion, which includes $20 billion in indirect costs and $30 billion in direct health care expenditures. These costs can be expected to continue to rise with this progressive disease. Costs increase with increasing severity of disease, and hospital stays account for the majority of these costs [40].

The global COPD market in Europe is valued at approximately €1.5 billion [41]. This growing market is becoming a major concern in decision making about pricing and reimbursement for the stakeholders in the healthcare systems. Available treatments for COPD are mainly symptomatic, and the near-term pipeline for COPD is mainly constituted by improved versions of currently used agents, alone or in combinations. For a new drug, it is necessary to determine whether the increase in cost is justified by the resultant improvement in patient-centered outcomes.

However, new pharmacotherapy in COPD has commonly limited additional efficacy versus their comparator as evaluated through the key clinical outcomes recommended by the European Agency for the Evaluation of Medicinal Products (EMEA). These clinical outcomes, for which the minimal clinically important difference is not always definitely established and which weakly reflect patient-related outcomes [42], are a major issue for the development of new drugs in COPD. The main criteria for drug development in COPD are about to be reconsidered by the EMEA [43]. In addition, the demonstration of product value during drug development faces the limitations of clinical trial designs, which may lead to an underestimation of costs compared with what would occur in a more naturalistic setting, especially considering the small and highly selected fraction of the COPD patient population included in these trials [44, 45]. Treatment guidelines in COPD are mainly based on evidence from the clinical trials conducted by the pharmaceutical industry. Deviation from these guidelines frequently occurs in general practice, resulting in extra costs that could extend to more than €500 per patient per year in patients with moderate COPD [46]. The economic evaluation for the decision to include a new treatment into the reimbursed package of a health insurer requires the use of final outcomes, such as life-years gained, improvement in generic quality of life and quality-associated life years (QALYs).

The cost-effectiveness of a new drug can only be assessed with regard to the maximum that decision makers are willing to pay for an exacerbation-free month, a QALY or another unit of effect. However, this information is not known in European countries except the UK. In a recent study, the analysis of the economic data from the TORCH study suggested that, based on costs for medication and primary and secondary care resources, the trial-wide point estimate for the cost per QALY compared with placebo was $43,600 for salmeterol/fluticasone combination with less favorable estimates for the single components. In the UK, it is commonly considered that

treatments falling below £20,000 per QALY are likely to be considered cost-effective. At a threshold willingness to pay for a QALY of $50,000 (conventional value in the USA), the likelihood for the combination treatment, salmeterol and fluticasone being cost-effective is ~0.93, 0.01 and 0.03, respectively, in the Western European region, suggesting that the combination should be preferred to monotherapies on the grounds of cost-effectiveness [47]. In the OPTIMAL trial, the association of the salmeterol/fluticasone combination with tiotropium improved some health outcomes, including the number of exacerbations requiring hospitalizations versus tiotropium alone, but the incremental cost-effectiveness ratio per QALY (from $145,000 to $243,000) compared with tiotropium alone suggested that monotherapy with tiotropium is the most cost-effective choice [48].

Conclusion

Substantial unmet needs remain in COPD and improved insight is required into the pathophysiology and effective treatments. From a diagnostic point of view, specific disease biomarkers, improved methods for early detection and diagnosis of exacerbations, and enhanced understanding of the relations between COPD and comorbidities would be helpful. Additionally, an important question that so far remains unanswered is whether different phenotypes of the disease exist and, if so, whether they respond differently to treatment.

Research is being done into new compounds to treat COPD [49]. Roflumilast, an oral specific phosphodiesterase 4 inhibitors, improved postbronchodilator FEV_1 by about 48 mL and was associated with a 17% reduction in the frequency of exacerbations in patients with GOLD stage 3–4 COPD and history of exacerbations, cough, and sputum changes, but had no effect on health-related quality of life or systemic inflammation [50]. Similar effects were seen in patients who received roflumilast in addition to salmeterol or tiotropium [51]. Indacaterol is a new, once-daily, long acting β2 agonist that provides sustained bronchodilation with an acceptable safety profile [52, 53]. Improvements in FEV_1 of 160–170 mL have been reported. Several new, once-daily, long-acting anticholinergic agents and β2 agonists are under development and being tested alone and in combination, with each other and with once daily inhaled steroids. Additionally, agents that possess simultaneous anticholinergic and β2-agonist activities (muscarinic antagonist β2 agonists) are being developed [54]. These latter agents will probably improve symptomatic control, but it seems unlikely that they will modify disease substantially more than available agents. By contrast, enhanced disease modification is expected from a range of novel inflammatory blockers that includes inhibitors of phosphodiesterase 4, agents targeting CD8+ T cells[49], and inhibitors of NF-κB,142 chemokine-receptors 2 and 3,142,148 T-helper-17 cells [49], and MAP kinase p38[49,55]. Finally, entirely new care models need to be developed for patients with COPD as well as other chronic diseases. In view of the comorbidities frequently seen in patients with COPD, new models for multidisciplinary care, clinical pathways, self-management [56], teleconsultating [57], telemonitoring, and rehabilitation are required.

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