Chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease affects millions of people, has a major impact on quality of life and has become an important cause of death worldwide. Over the past decade, a better understanding of COPD has been gained, while research into new therapies and treatment strategies has provided significant treatment advances. In this article, the different therapeutic classes that are available for COPD will be reviewed, including combination therapy and the recommended stepwise approach for disease management.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality globally.[1] A recent study suggests a global prevalence of approximately 10%.[2] Interestingly, Cape Town had the highest global prevalence of 22.2% in men and 8.5% in women.[2] COPD was thought to develop in only 15% of smokers. However, it is now realised that this is an underestimation because COPD is both under-recognised and undiagnosed. Many patients accept the limitations associated with disease progression as natural for a person who has smoked.[2-5] The incidence of COPD in non-smokers is estimated to be 5% or less.[6] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) estimates that COPD will be the third most common cause of death worldwide by 2020.[1]

Understanding chronic obstructive pulmonary disease

COPD is defined as a preventable and treatable disease state that is characterised by airflow limitation that is not fully reversible.[1] Airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to inhaled noxious particles or gases, primarily caused by cigarette smoking.[1-3]

COPD encompasses the two distinct but often related processes of chronic bronchitis and emphysema, both of which result in structural changes that limit airflow: [1,7]

- *Chronic bronchitis:* Chronic bronchitis is an inflammatory condition of the large and small airways that results in mucous gland enlargement and mucous hypersecretion.[7] It is diagnosed when a patient, in the absence of other causes, has a chronic, productive cough for at least three months of the year for two or more consecutive years.[8] It often precedes airflow limitation by many years.[8]
- *Emphysema:* Emphysema involves destruction of the lung parenchyma with dilation and destruction of the respiratory bronchioles.[7] These changes in the anatomy of the lung result in deterioration of gas exchange and impaired ventilation.[6]

Diagnosis

COPD should be considered in any individual who has dyspnoea, chronic cough or sputum production and/or who has a history of exposure to risk factors for the disease, especially cigarette smoking (Table I).

The diagnosis of airflow limitation is confirmed by means of spirometry: [1,8]

- Post-bronchodilator forced expiratory volume in one second (FEV1) < 80% of the predicted value.
- Ratio of FEV1/forced vital capacity < 70%.

Table I: Key indicators for considering a chronic obstructive pulmonary disease diagnosis[1]

Indicators are not diagnostic, but multiple key indicators increase the probability of a diagnosis of COPD:

- Dyspnoea that is progressive, usually worse with exercise, persistent (present every day) and described as “gasping”, “heaviness” or “increased effort to breathe”.
- A chronic cough may be intermittent and unproductive.
- Any pattern of chronic sputum production may indicate COPD.
- A history of exposure to risk factors, such as tobacco smoke, occupational dust and chemicals, and smoke from home cooking and from heating fuel.

Table II: Classification of severity of chronic obstructive pulmonary disease[9]

Stage	Characteristics
I: Mild COPD	Mild airflow limitation FEV1/FVC < 70% FEV1 ≥ 80% predicted With or without chronic symptoms
II: Moderate COPD	Worsening airflow limitation FEV1/FVC < 70% 50% ≤ FEV1 < 80% predicted With or without chronic symptoms
III: Severe COPD	Further worsening of airflow limitation FEV_1/FVC < 70% 30% ≤ FEV1 < 50% predicted With or without chronic symptoms (coughing and sputum production)
IV: Very severe COPD	FEV1/FVC < 70% FEV1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure At this stage, quality of life is significantly impaired and exacerbations may be life-threatening

COPD: chronic obstructive pulmonary disease, FEV1: forced expiratory volume in one second, FVC: forced vital capacity
Note: The Stage 0: At risk stage is no longer included in the revised 2009 Global Initiative for Chronic Obstructive Lung Disease Guidelines as there is incomplete evidence that individuals who meet the definition of "at risk" (chronic coughing and sputum production, and normal spirometry) necessarily progress to Stage I. Nonetheless, the importance of the public health message that chronic coughing and sputum are not normal is unchanged.

Stages

A staging system for COPD severity has been established by GOLD that defines disease severity according to airflow limitation (Table II).

Management

Lifestyle

All patients should be encouraged to lead a healthy lifestyle and exercise regularly.[2] Symptomatic patients may benefit from an exercise programme devised by a physiotherapist.

Smoking is the major cause of COPD. Therefore, smoking cessation is the most important component of therapy for patients who still smoke.[1-6] Smoking cessation slows the decrease in lung function in patients with established disease.[1] Pharmacists can make a valuable contribution in this area.

Pharmacotherapy

The main aims of therapy are to reduce exacerbations and related hospitalisation, improve quality of life and reduce the rate of decline in lung function (measured as FEV1) (Table III).

Table III: Goals of chronic obstructive pulmonary disease management[1]

- Relieve symptoms.
- Prevent disease progression.
- Improve exercise tolerance.
- Improve health status.
- Prevent and treat complications.
- Prevent and treat exacerbations.
- Reduce mortality.
- Prevent or minimise side-effects from treatment.

Recommended treatment strategy

GOLD recommends a stepwise increase in treatment, depending on the severity of the disease and individual response (Table IV).

Bronchodilators

Bronchodilators are the cornerstone of therapy for COPD and include beta 2 agonists and anticholinergics, given alone or in combination, depending on the severity of disease and response to therapy.

All symptomatic patients with COPD should be prescribed a short-acting bronchodilator to use on an as-needed basis for the relief of persistent or worsening symptoms (Step 1).[1,4,9] A regular, scheduled, long-acting bronchodilator should be added if symptoms are inadequately controlled with a short-acting bronchodilator to prevent or reduce symptoms (Step 2).[1,4,9] This is more effective and convenient, although more expensive than treatment with short-acting bronchodilators.[1,2] Combining bronchodilators may improve efficacy and decrease the risk of side-effects, rather than increasing the dose of a single bronchodilator.[1]

Bronchodilators have consistently been shown to induce long-term improvements in symptoms, exercise capacity and airflow limitation, even where there is no spirometric improvement following a single-dose test.[4] In cases of stable COPD, the choice between a beta 2 agonist and an anticholinergic depends on availability and individual response in terms of symptom relief and side-effects.[9,10] Individual response to the various bronchodilators cannot be reliably predicted. Therefore, a process of trial and review is recommended.

Most bronchodilators can be administered by inhalation, orally or intravenously. Inhalation is the recommended delivery method as it maximises the bronchodilator's direct effect on the airways, while minimising the systemic effects.[1,4]

Table IV: Therapy at each stage of chronic obstructive pulmonary disease[9]

Mild	Short-acting bronchodilator (when needed)			
Moderate		Add regular treatment with one or more long-acting bronchodilators		
Severe			Add inhaled corticosteroids if repeated exacerbations	
Very Severe				Add long-term oxygen if chronic respiratory failure

A metered dose inhaler (MDI), dry powder inhaler (DPI) or a nebuliser can be used to deliver the medication by inhalation.[4] When used correctly, MDIs and DPIs achieve a bronchodilator response equivalent to that achieved with a nebuliser.[4] Some COPD patients cannot effectively activate MDIs and pharmacists are well placed to help patients master this technique. If this is not possible, use of a spacer or nebuliser may help.[2] Prior to exertion, education regarding the purpose and dosing of medications and timing of short-acting bronchodilators is essential.[4]

- *Inhaled beta 2 agonists*

Mode of action: Inhaled beta 2 agonists activate beta 2 adrenergic receptors on the surface of smooth muscle cells which increases cyclic adenoside monophosphate (AMP) and smooth muscle relaxation.[3]

Initially, short-acting beta 2 agonists, e.g. salbutamol, fenoterol and terbutaline, should be tried for symptomatic relief in patients with mild intermittent symptoms, as they provide rapid relief and have a low incidence of side-effects.[2,3,6] They improve symptoms and lung function, and if used before exercise, can improve exercise tolerance.[4,6]

Long-acting beta 2 agonists, e.g. salmeterol and formoterol, have a greater duration of effect than short-acting bronchodilators (more than 12 hours vs. 4-6 hours), with no loss of effect with long-term use.[9] Evidence suggests that long-acting beta 2 agonist monotherapy also results in greater improvement of symptoms, fewer exacerbations, reduced rescue medicine use and improved overall health status, compared with short-acting bronchodilator therapy.[11]

Safety: Overuse can result in tremors and reflex tachycardia.[4] Hypokalaemia can also occur in extreme cases and should be monitored in at-risk patients.[4]

- *Anticholinergic bronchodilators*

Mode of action: Anticholinergic bronchodilators compete with acetylcholine for muscarinic receptors in the lung and thereby reduce airway tone and relieve bronchospasm.[6] The location and distribution of muscarinic receptors in the lung differ from that of beta receptors and may have a more important functional role to play in the elderly and smokers.

Short-acting anticholinergics, e.g. ipratropium, have been shown to have equivalent or superior effects when compared with beta 2 agonists in patients with stable COPD.[2,10] Ipratropium has a slower onset of action than short-acting beta 2 agonists (approximately 40 minutes vs. 10-20 minutes), but a longer duration (9 hours vs. 4-6 hours).[2,6,11]

A once-daily preparation of long-acting anticholinergics, e.g. tiotropium, has been shown to have significant clinical

benefits in COPD. Compared to placebo, tiotropium reduces exacerbations, improves health-related quality of life and symptoms in patients with moderately severe COPD.[3]

The Understanding the Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study compared four years of therapy with either tiotropium or placebo in almost 6 000 patients and showed a significant reduction in the frequency of COPD exacerbations, hospitalisations and an improvement in quality of life.[7,11] However, although mean improvements in FEV1 with tiotropium were superior to placebo and were maintained throughout the study, the differences were not statistically significant.[7, 11]

Safety: Anticholinergics are poorly absorbed, which limits systemic adverse effects. The most frequently reported side-effect is dryness of the mouth. More serious effects appear to be rare.[9] There have been recent reports of elevations in cardiovascular risk, although these findings have not been fully elucidated and this risk remains uncertain.[4,11]

- *Theophylline*

Mode of action: Theophylline is a non-specific phosphodiesterase inhibitor that increases cyclic AMP within airway smooth muscle, causing bronchodilation.[3]

Theophylline is of value in patients who are noncompliant or who cannot use aerosol therapy optimally.[3] Inhaled bronchodilators are preferred when available because of potential toxicity of theophylline.[1]

Safety: It is hepatically metabolised and any process that interferes with liver function can rapidly change theophylline levels. Many drugs interact with theophylline.[4] Close monitoring of blood levels is required and theophylline levels of 8-13 µg/ml are recommended.[2-4,10] Adverse effects include anxiety, tremors, insomnia, nausea, cardiac arrhythmia and seizures.[2]

Combination bronchodilator therapy is generally preferred as this provides the patient with advantages that are unique to each medication and achieves a greater bronchodilator response than either one alone.[1-4] Studies have reported on the complementary effects of ipratropium and short-acting beta 2 agonists and on those between tiotropium and long-acting beta 2 agonists.[9,12]

Corticosteroids

Mode of action: Corticosteroids are potent anti-inflammatory agents that affect the inflammatory cascade at multiple points.[2-3]

- *Inhaled corticosteroids*

COPD is characterised by both airways and systemic inflammation and inhaled corticosteroids (ICS) may reduce this inflammation.[4] Regular treatment with ICS is only appropriate for symptomatic patients with FEV < 50% predicted and repeated exacerbations.[7,9] They should be used as part of a combined regimen and should not be used as sole therapy for COPD.[4]

Data suggest that ICS decrease exacerbations and slow the rate of loss of health-related quality of life, but appear to have little impact on the long-term decline in FEV1 and mortality.[2, 4,9,11]

- *Systemic corticosteroids*

Systemic corticosteroids are used to treat exacerbations of COPD. However, long-term systemic use can have significant adverse effects and has been associated with an increase in morbidity and mortality. Therefore, it is not recommended.[4,9]

- *Inhaled corticosteroids combination therapy with bronchodilators*

Typically, ICS are used in combination with long-acting bronchodilators for patients in GOLD Stage III or IV, who have significant symptoms or repeated exacerbations, despite following an optimal bronchodilator regimen (Step 3).[1,4] Such combination therapy has been shown to significantly reduce the frequency of exacerbations and improve health status compared to monotherapy.[4]

Effect on mortality: The Towards a Revolution in COPD Health (TORCH) was a three-year study of 6 184 patients with severe COPD mostly, randomised to salmeterol or fluticasone as monotherapy, or in combination. Interestingly, combination therapy showed a trend towards a decrease in mortality (although this reduction did not achieve statistical significance) and significantly improved health status, rate of exacerbations and also produced a sustained increase in lung function in all groups compared with placebo.[4,5]

Triple-inhaler therapy with a long-acting beta 2 agonist, long-acting anticholinergic plus an ICS, is often used and studies evaluating this combination are underway.[4]

Safety: Aside from oral candidiasis and hoarseness, the systemic adverse effects of ICS at standard doses are negligible.[2,3,11] An increased incidence of pneumonia has been observed in some clinical studies using ICS therapy.[7,11]

Other pharmacological therapies

- *Mucolytics:* Thick, tenacious secretions can be a major problem with patients with COPD. N-acetylcysteine has anti-oxidant and mucokinetic properties and is used to treat patients with COPD.[2] However, the efficacy of mucolytic agents remains controversial and further research in this area is needed.[1,2]
- *Vaccinations:* All COPD patients should receive an annual

influenza vaccine as this can reduce serious illness and death by about 50%.[1] A pneumococcal vaccine is also recommended.[6, 10,13]

- *Monitoring:* It is important to determine whether an adequate response to therapy has been achieved[4] by taking into account the symptoms (dyspnoea, exercise tolerance, coughing and sputum production), airflow (spirometry), the mount of "rescue" medication used, i.e. short-acting bronchodilators and the frequency of exacerbations.

Nonpharmacological therapies

- *Patient education:*[13] Patient education should cover medication and lifestyle issues to prevent exacerbations, how to recognise the early signs of an exacerbation (breathlessness, more sputum, coloured sputum and/or fever) and how to respond to an exacerbation. Some patients may be prescribed oral corticosteroids and antibiotics for use to self-manage an acute exacerbation and should be informed about this.
- *Pulmonary rehabilitation:* Pulmonary rehabilitation includes oxygen and inhaler use, breathing techniques, nutritional support and most importantly exercise conditioning.[3] Studies have shown unequivocal improvements in exercise capacity, severity of dyspnoea and health related quality of life.[7] Patients with moderate to moderately severe disease are the best candidates, for whom the end stages of respiratory failure can be prevented.[3]
- *Supplemental oxygen therapy:* Studies have shown that supplemental oxygen therapy improves survival in patients with hypoxemic COPD (Step 4).[3] Other benefits include reductions in polycythaemia, pulmonary arterial pressures, dyspnoea, hypoxaemia during sleep and reduced nocturnal arrhythmias.[3]
- *Acute exacerbation:* Acute exacerbation is an event in the course of COPD that is characterised by a change in the patient's baseline dyspnoea, coughing and/or sputum, is sufficient to warrant a change in management and is an importance clinical event in COPD.[1-3] The most common causes of an exacerbation are chest infection and air pollution, but the cause of approximately one third of infections cannot be identified.[1]

The pharmacological management of exacerbations is initiated with the same therapeutic agents that are available for long-term management.[3]The most important agents include anticholinergics and beta agonists by nebulisation.[3] Several trials have proven the usefulness of oral corticosteroids.[3] However, avoid prolonged (> 2 weeks) or high-dose therapy.

Colonisation or chronic infections of the lower airways is common with *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis* in patients with COPD.[2] Empiric antimicrobial therapy is recommended in patients with evidence of an infectious process.[1-2] Some patients may need temporary oxygen administration.[3]

Exacerbations should be prevented where possible, and treated aggressively as they have a prolonged and intense effect on health related quality of life and can result in accelerated loss of lung function.[3]

Conclusion

Research in the management of COPD has provided a wealth of new information, particularly on combination therapy. A clear understanding of the various classes of medication that are available for this disease is needed, as well as about their impact on the disease, and how they can be combined so as to optimise individual COPD management.

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