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 we have gained a better understanding of COPD and research into new therapies and treatment strategies has provided significant treatment advances. In this article we review the different therapeutic classes available for COPD, including combination therapy and the recommended stepwise approach for disease management.

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

Understanding COPD
COPD is defined as a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. 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.

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

- **Chronic bronchitis** is an inflammatory condition of the large and small airways that results in mucous gland enlargement and mucous hypersecretion. 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. It often precedes airflow limitation by many years.

- **Emphysema** involves destruction of the lung parenchyma with dilation and destruction of the respiratory bronchioles. These changes in the anatomy of the lung results in deterioration of gas exchange and impaired ventilation.

Diagnosis of COPD
COPD should be considered in any individual who has dyspnoea, chronic cough or sputum production and/or 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:

- Post-bronchodilator forced expiratory volume in 1 second (FEV₁) < 80% of the predicted value
- Ratio of FEV₁/FVC (forced vital capacity) < 70%

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

Table I: Key indicators for considering a COPD diagnosis

<table>
<thead>
<tr>
<th>Indicators are not diagnostic but multiple key indicators increase the probability of a diagnosis of COPD:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyspnoea</strong> that is: progressive usually worse with exercise persistent (present every day) described as “gasping”, “heaviness” or “increased effort to breathe”</td>
</tr>
<tr>
<td><strong>Chronic cough</strong>: may be intermittent and unproductive</td>
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<tr>
<td><strong>Chronic sputum production</strong>: any pattern may indicate COPD</td>
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<tr>
<td><strong>History of exposure to risk factors</strong>: tobacco smoke occupational dust and chemicals smoke from home cooking and heating fuel</td>
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Management

Lifestyle
All patients should be encouraged to lead a healthy lifestyle and exercise regularly. Symptomatic patients may benefit from an exercise programme from a physiotherapist.

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

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

Table II: Classification of severity of COPD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mild COPD</td>
<td>• Mild airflow limitation</td>
</tr>
<tr>
<td></td>
<td>• FEV₁/FVC &lt; 70%</td>
</tr>
<tr>
<td></td>
<td>• FEV₁ ≥ 80% predicted</td>
</tr>
<tr>
<td></td>
<td>• With or without chronic symptoms</td>
</tr>
<tr>
<td>II: Moderate COPD</td>
<td>• Worsening airflow limitation</td>
</tr>
<tr>
<td></td>
<td>• FEV₁/FVC &lt; 70%</td>
</tr>
<tr>
<td></td>
<td>• 50%≤FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td></td>
<td>• With or without chronic symptoms</td>
</tr>
<tr>
<td>III: Severe COPD</td>
<td>• Further worsening of airflow limitation</td>
</tr>
<tr>
<td></td>
<td>• FEV₁/FVC &lt; 70%</td>
</tr>
<tr>
<td></td>
<td>• 30%≤FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td></td>
<td>• With or without chronic symptoms (cough, sputum production)</td>
</tr>
<tr>
<td>IV: Very severe COPD</td>
<td>• FEV₁/FVC &lt; 70%</td>
</tr>
<tr>
<td></td>
<td>• FEV₁&lt; 30% predicted or FEV₁ &lt; 50% predicted plus chronic respiratory failure</td>
</tr>
<tr>
<td></td>
<td>• At this stage quality of life is significantly impaired and exacerbations may be life threatening</td>
</tr>
</tbody>
</table>

Note: The Stage 0 – At risk stage, is no longer included in the revised 2009 GOLD Guidelines, as there is incomplete evidence that the individuals who meet the definition of ‘At Risk’ (chronic cough and sputum production, normal spirometry) necessarily progress to Stage I. Nonetheless, the importance of the public health message that chronic cough and sputum are not normal is unchanged.

Table III: Goals of COPD management

- 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

Table IV: Therapy at each stage of COPD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Short-acting bronchodilator (when needed)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Add regular treatment with one or more long-acting bronchodilators</td>
</tr>
<tr>
<td>Severe</td>
<td>Add inhaled corticosteroids if repeated exacerbations</td>
</tr>
<tr>
<td>Very Severe</td>
<td>Add long-term oxygen if chronic respiratory failure</td>
</tr>
</tbody>
</table>

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

1. Bronchodilators
Bronchodilators are the cornerstone of therapy for COPD and include β₂-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 relief of persistent or worsening symptoms (step 1). 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). This is more effective and convenient, although more expensive than treatment with short-acting bronchodilators. Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

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.

In stable COPD the choice between β₂-agonist and anticholinergic depends on availability, individual response in terms of symptom relief and side effects. 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 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 Education regarding the purpose and dosing of medications and timing of short-acting bronchodilators prior to exertion is essential.4

• **Inhaled ß2-agonists**
  **Mode of action:** activate ß2-adrenergic receptors on the surface of smooth muscle cells which increases cyclic AMP and smooth muscle relaxation.3

  **Short-acting ß2-agonists** e.g. salbutamol, fenoterol and terbutaline should be tried initially 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 ß2-agonists (LABAs)** e.g. salmeterol and formoterol have a greater duration of effect than short-acting bronchodilators (more than 12 h vs 4–6 h), with no loss of effect with long-term use.6 Evidence suggests that LABA 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.9

  **Safety:** Overuse can result in tremor and reflex tachycardia.4 Hypokalaemia can also occur in extreme cases and should be monitored in patients at risk.4

• **Anticholinergic bronchodilators**
  **Mode of action:** They compete with acetylcholine for muscarinic receptors in the lung and thereby reduce airway tone and relieve bronchospasm.4 The location and distribution of muscarinic receptors in the lung differ from that of beta receptors and may have a more important functional role in the elderly and smokers.

  **Short-acting anticholinergics** e.g. ipratropium have been shown to have equivalent or superior effects when compared with ß2-agonists in patients with stable COPD.2,13 Ipratropium has a slower onset of action than short-acting ß2-agonists (approx 40 min vs 10–20 min) but a longer duration (9 hrs vs 4–6 hrs).2,6,9

  **Long-acting anticholinergics** e.g. tiotropium – a once daily preparation that 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

  **Theophylline**
  **Mode of action:** Theophylline is a non-specific phosphodiesterase inhibitor that increases cyclic AMP within airway smooth muscle causing bronchodilation.5 Theophylline is of value in patients who are non-compliant or who cannot use aerosol therapy optimally.2 Due to its potential toxicity, inhaled bronchodilators are preferred when available.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 mcg/ml are recommended.2,4,11 Adverse effects include anxiety, tremor, insomnia, nausea, cardiac arrhythmia and seizures.2

  **Combination bronchodilator therapy** is generally preferred as this provides the patient with advantages unique to each medication and achieves a greater bronchodilator response than either one alone.1,4 Studies have reported complementary effects of ipratropium and short-acting ß2-agonists and between tiotropium and LABA.2,13

2. **Corticosteroids**
   **Mode of action:** Potent anti-inflammatory agents that affect the inflammatory cascade at multiple points.2,3

   **Inhaled corticosteroids (ICS)**
   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 FEV1 < 50% predicted and repeated exacerbations.7,15 They should be used as part of a combined regimen and should NOT be used as sole therapy for COPD.4

   Data suggests 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.2,4,8,10
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 and is therefore not recommended.4,10

ICS combination therapy with bronchodilators
ICS are typically used in combination with long-acting bronchodilators for patients in GOLD stage III or IV, who have significant symptoms or repeated exacerbations despite 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 3 year study of 6 184 patients with mostly severe COPD randomised to salmeterol or fluticasone as monotherapy or in combination. Combination therapy interestingly 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 LABA, 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.2,3,9 An increased incidence of pneumonia has been observed in some clinical studies using ICS therapy.7,9

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 annual influenza vaccine as this can reduce serious illness and death by about 50%.1 Pneumococcal vaccine is also recommended.6,11-12

Monitoring
It is important to determine whether an adequate response to therapy has been achieved:
- Symptoms (dyspnea, exercise tolerance, cough, sputum production)
- Airflow (spirometry)
- Amount of ‘rescue’ medication used i.e. short-acting bronchodilators
- Frequency of exacerbations

Non-pharmacologic therapies
- Pulmonary rehabilitation includes oxygen and inhaler use,

Patient education:
- Medication and lifestyle issues to prevent exacerbations
- How to recognise early signs of an exacerbation (breathlessness, more sputum, coloured sputum and/or fever)
- 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 well educated

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.1 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 it improves survival in patients with hypoxemic COPD (step 4).3
- Other benefits include: reductions in polycythemia, pulmonary arterial pressures, dyspnoea, hypoxemia during sleep and reduced nocturnal arrhythmias.3

Acute exacerbation
Acute exacerbation is an event in the course of COPD characterised by a change in the patient’s baseline dyspnoea, cough and/or sputum sufficient to warrant a change in management and is an importance clinical event in COPD.1,2 The most common causes of an exacerbation are chest infection and air pollution, but the cause of about one third of infections cannot be identified.1

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

In patients with COPD colonisation or chronic infections of the lower airways is common with Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.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 regarding combination therapy. We need to have a clear understanding of the various classes of medication available for this disease, their impact on the disease and how they can be combined so as to optimise individual COPD management.

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