REVIEW ARTICLE

Chronic Obstructive Pulmonary Disease Part II

A Review of Pharmacological Managements of Chronic Obstructive Pulmonary Disease

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a disease which warrants a great attention due to the mortality and morbidity caused by COPD. Once a patient has been diagnosed with COPD, a clear plan of care has to be established. Pharmacological management is usually the initial treatment in addition to prevention. COPD exacerbations impair the patient's quality of life and decrease their health status. The decision to start treatment in patient with COPD should be based on the number of symptoms and the risk for exacerbations. Exacerbations will eventually occur in most patients with COPD. The prevention of exacerbations is one of the main goals in the management of COPD. Early recognition and prompt treatment of COPD exacerbation, is very beneficial to the overall outcome of the patient. Stable COPD has several treatment options available based on the stages and so patients within the same stage may be on different treatment regimens. The management of COPD is stepwise. The aim of pharmacological management of COPD is to decrease symptoms and complications. For patients with stable COPD, the treatment goals are to reduce the risk of exacerbation, decrease symptoms and improve exercise tolerance aiming at improving general health and quality of life. This article details the pharmacological management of COPD.

Introduction

COPD management requires a multidisciplinary approach. Once a diagnosis of COPD is made, there is no intervention, except for lung transplant, that will prevent the progression of the disease or decrease mortality. [1] The different aspects that have to be evaluated and managed. Patients have to be assessed and staged. A baseline spirometry has to be obtained, so that the progression of the disease can be monitored objectively. Risk factors have to be identified and reduced or eliminated. Even though the patients are staged to determine the severity of their COPD, the treatment has to be individualized. Stable COPD has several treatment options available based on the stages and so patients within the same stage may be on different treatment regimens.[1-4] COPD exacerbations impair the patient's quality of life and decrease their health status. The prevention of exacerbations is one of the main goals in the management of COPD. However, patients will have exacerbations, and the early recognition and prompt treatment of COPD exacerbation, is very beneficial to the overall outcome of the patient.[1] The management of COPD includes assessment and monitoring of the disease, risk factor reduction or elimination in cases of tobacco use, reducing exacerbations and manage-ment of exacerbations.

The Components of COPD management

An early diagnosis is paramount to the management of COPD. A thorough history with attention to exposure to risk factors must be completed. The presence of intrinsic risk factors such as alpha 1 antitrypsin deficiency must be thoroughly evaluated.[1,2,5] Spirometry evidence of airway limitations with or without symptoms (chronic cough, sputum, dyspnea) with FEV1/FVC <70% and post bronchodilator-FEV1<80% predicted also have to be evaluated.[1] An ABG is required if FEV1 <40% predicted or there are clinical signs suggestive of right heart or respiratory failure.

Risk factors reduction is an important component of COPD evaluation and management. Risk factor management is paramount in preventing the onset and progression of COPD. Decrease exposure to air pollutants, tobacco smoke, occupational dusts and chemicals pollutants is required.[1] Smoking cessation is the most effective and cost savings way to prevent the onset and progression of COPD.[6] Smoking cessation can be approached in several ways ranging from counselling to pharmacological interventions.[1,2]

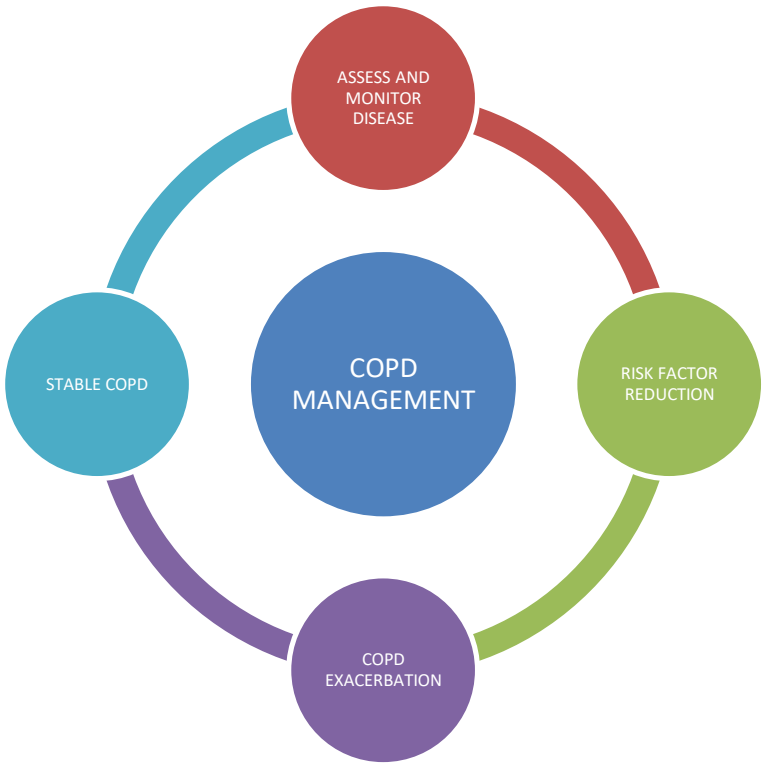
Management of COPD requires a team effort. Patient education and smoking cessation are indispensable components in the management of COPD. Exercise training to improve exercise tolerance and decreases both dyspnea and fatigue as well as Long term oxygen therapy, (>15L/d) to decrease mortality.[5]

The goal of pharmacotherapy is to decrease symptoms and complication. Bronchodilators, either scheduled or on as needed bases. Inhaled steroids are used in patients with symptomatic COPD with spirometry response to steroids or FEV1 <50% predicted and repeat exacerbations that need antibiotics and oral steroids. Chronic steroid therapy is not good in the long term.

Finally identify the exacerbating factors like infection or air pollution and treat, eliminate

or reduce accordingly. A third of COPD exacerbations have no identifiable cause.

Figure 1: Components of COPD management



The goals of care for the management of COPD include:

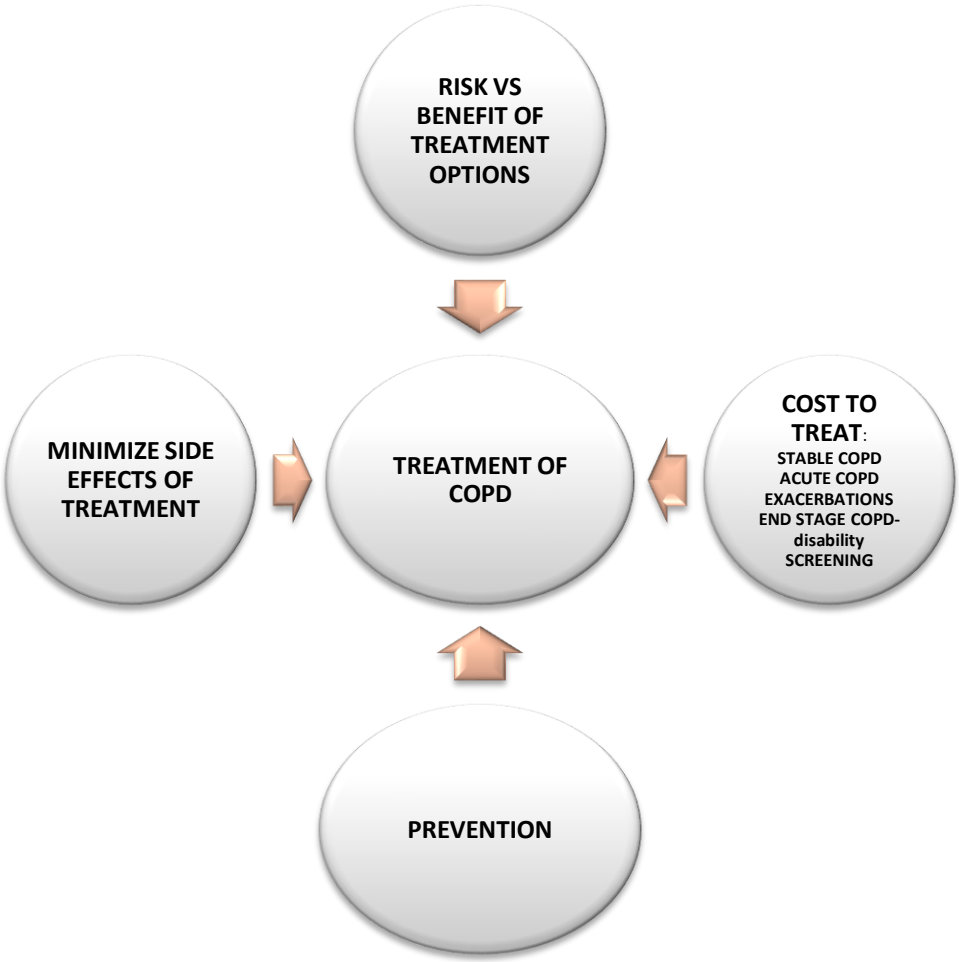
- Prevent COPD from progressing and thus reducing long term lung function decline
- Prevent and treat exacerbations
- Prevent and treat complications
- Relieve symptoms like disabling shortness of breath
- Improve exercise tolerance
- Improve health status-health related quality of life, reduce hospitalizations
- Reduce Mortality

The overall goal of COPD management is to improve the patient's functional status and thus their health-related quality of life in a cost-effective manner. [1,2,7] Treatment should be individualized and aimed at preventing or rapidly treating exacerbations, reducing the long term functional decline associated with COPD and reducing hospitalizations and mortality.

Figure 1 demonstrated the factors that should be considered in the overall treatment of patients with COPD. These goals should be achieved with treatments that will cause the minimum side effects for that patient. Comorbidities tend to complicate the treatment of COPD and are a major aspect also in the management of COPD.

To achieve the overall goals of care in the management of COPD a multifaceted approach in treatment must be taken. The core of this approach is patient education and health care follow up, with the aim of reducing hospital visits.[1] COPD symptoms need to be controlled and exacerbations must be prevented.

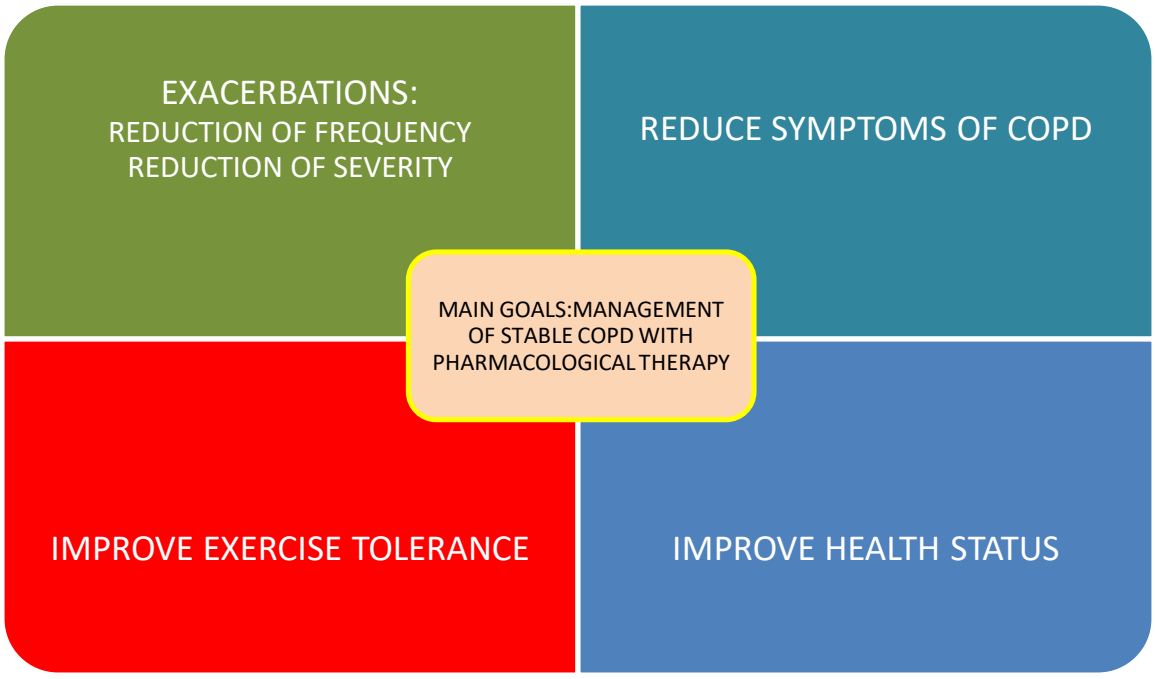
Figure 2: Factors to Consider When Deciding on Treatment Options



Management of Stable COPD

The decision to start treatment in patients with stable COPD should be based on the number of symptoms and the risk for exacerbations. The management of stable COPD is usually in a stepwise progression. Treatment is adjusted based on whether the patient continues to have exacerbations while on maintenance therapy and if the symptoms of breathlessness or exercise limitations are present. The main goals in starting pharmacological managements in stable COPD are to reduce symptoms, reduce the frequency and severity of exacerbations, and to improve exercise tolerance and overall health as noted figure 3.

Figure 3: Main Goals in the Management of Stable COPD with pharmacological therapy

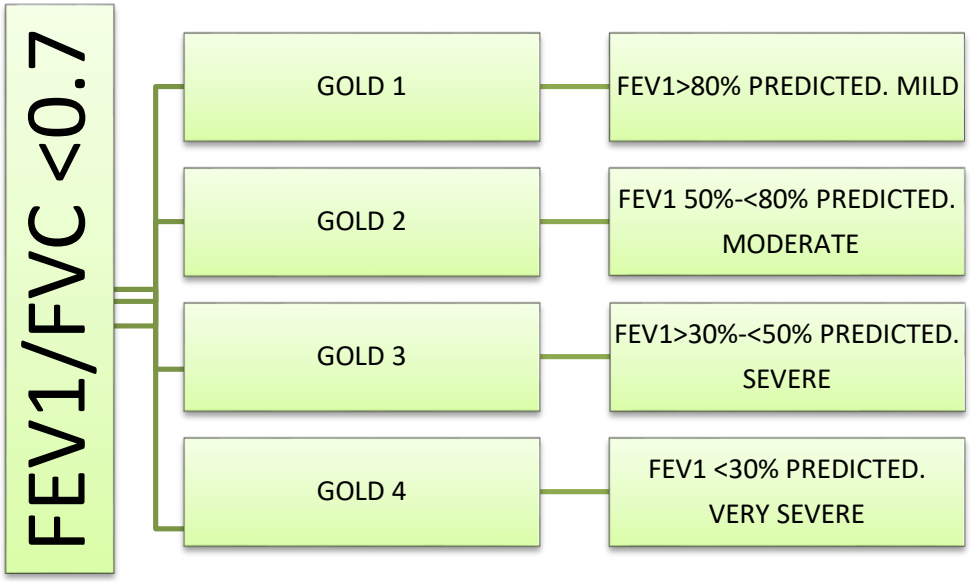


Assessment of symptoms

Prior to initiating management for stable COPD, the symptoms have to be appropriately assessed. The MMRC dyspnea scale only measures dyspnea and so other more comprehensive scales such as the CAT scales and the COPD Control Questionnaire have been developed. These assessments are simple, self-administered assessment tools that measure health status in addition to shortness of breath. They are reliable, comprehensive, reproducible and applicable worldwide. [1,8,9]

FEV1 is needed for the initial assessment. Based on the FEV1 patients will be placed into GOLD 1-4 based on the FEV1.

Figure 4: GOLD Classification of COPD based on FEV1



The Modified Medical Research Council (MMRC) Dyspnea Scale only measures dyspnea and so other more comprehensive scales such as the COPD Assessment Test (CAT) scales and the COPD Control Questionnaire

Table 1: MMRC: The patients are required to assess their level of breathlessness and then graded.[10,11]

STAGE 0	I only get breathless with strenuous exercise
STAGE 1	I get short of breath when hurrying on level ground or walking up a slight hill
STAGE 2	On level ground, I walk slower than people of the same age because of breathlessness , or have to stop for breath when walking at my own pace
STAGE 3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
STAGE 4	I am too breathless to leave the house or I am breathless when dressing

Table 2: CAT[12-14]

- I never cough, 0 1 2 3 4 5 I cough all the time.
- I have no phlegm (mucus) in my chest at all, 0 1 2 3 4 5 My chest is completely full of phlegm
  My chest does not feel tight at all, 0 1 2 3 4 5 My chest feels very tight.
- When I walk up a hill or one flight of stairs I am not breathless, 0 1 2 3 4 5 When I walk up a hill or one flight of stairs I am very breathless.
- I am not limited doing any activities at home, 0 1 2 3 4 5 I am very limited doing activities at home.
- I am confident leaving my home despite my lung condition, 0 1 2 3 4 5 I am not at all confident leaving my home because of my lung.
- I sleep soundly, 0 1 2 3 4 5 I don't sleep soundly because of my lung condition.
- I have lots of energy, 0 1 2 3 4 5 I have no energy at all.

A more comprehensive assessment of the symptoms using the CAT-COPD Assessment Test or mMRC -Modified Medical Research Council Dyspnea Scale along with exacerbation history classifies the patient into GOLD ABCD as noted below.[1] Pharmacotherapy is based on 4 GOLD categories,

Category A

These patients are at low risk for exacerbations with one or less exacerbation in the previous year. They have mild or infrequent symptoms and they fall into the GOLD 1 or 2 spirometric category. These patients are best treated with a bronchodilator which can be a short acting bronchodilator (a beta agonist bronchodilator alone, or an anticholinergic bronchodilator alone) as needed or a long acting bronchodilator. Another option may be a combination of the short acting bronchodilators with a long acting anticholinergic or a long acting beta agonist. The alternative to these options is theophylline-which is not highly recommended. [1,2,6,15]

Category B

Patients in category B are more symptomatic and suffer from moderate to severe symptoms but are at low risk for exacerbations. They also had one or less exacerbation in the previous year and fall into the GOLD 1 or 2 spirometry categories. Initial therapy must include a long acting bronchodilator. In this category they are superior to taking only short-acting bronchodilators as needed. Short acting bronchodilators can be used for acute exacerbations and pulmonary rehabilitation. There is no evidence to support the use of any one long acting agent over another. The choice is individualized to the patient's tolerance and symptom relief. In patient with severe breathlessness, therapy may be initiated with two bronchodilators.

Alternatively, theophylline may be used.[1,15] Also evaluate patients for comorbidities that may add to their clinical presentation and impact their response to therapy.

Category C

Exacerbation risk is increased in these patients, they have two or more exacerbations per year, or they may have had one hospitalization for exacerbation. They fall into the GOLD 3 or 4 spirometric stages. Paradoxically, these patients have mild or infrequent symptoms. Again, short acting bronchodilators are used in an acute exacerbation.

It is recommended that initial therapy be a single long acting bronchodilator-a LAMA- as studies have shown that LAMA was superior in preventing COPD exacerbation in this group compared to LABA. A second choice would be to use a combination of two long acting agents or inhaled steroids and a long acting anticholinergic agent. Alternatively, if none of the above is available to patients, then a short acting bronchodilator and theophylline may be used.[1,2,15,16]

Category D

Patients are at high risk for exacerbations having more than two per year or at least one hospitalization for exacerbation. They are more symptomatic, and they fall into the GOLD 3 or 4 spirometric classes (1). These patients should be prescribed a short acting bronchodilator to use as needed. For patients with severe symptoms, with breathlessness and limitation of exercise, treatment may be initiated with a LAMA/LABA combination. In some patients first choice of therapy may be a combination of inhaled glucocorticoid (ICS) and a long-acting beta agonist. Patients with COPD and a history of asthma and or those with blood eosinophil counts>300cells/uL are the ones most likely to benefit from the combination of ICS/LABA.

Other options include the following: Inhaled steroids, a long-acting beta agonist and a long acting anticholinergic OR Inhaled steroids, a long acting beta agonist and a phosphodiesterase-4 inhibitor OR Long acting anticholinergic and a long acting beta agonist OR Long acting anticholinergic and a phosphodiesterase 4 inhibitor. Alternatively, carbocysteine, a short acting beta agonist and/ or a short acting anticholinergic or theophylline as well as surgical treatments may be considered.[1,2,6,15]

Patients must receive full education on the following in order to achieve the above mentioned goals for the pharmacological management of COPD:

- The nature of COPD
- The risk factors for progression of COPD-avoidance and management
- Their role in the management of their disease
- The role of the health care worker in the management of their disease

An extensive evaluation of the patient's smoking history, alpha1-antitrypsin levels if indicated and an evaluation of comorbidities are also key in determining the subsequent management of stable COPD.[1] A review of the patient should be done after a suitable interval. At that review, the patient should be

assessed as indicated in figure 1. Patients with COPD who are not responding to therapy and who continue to have symptoms or repeated exacerbations despite optimizing therapy, should be evaluated for other illnesses that could be contributing to their shortness of breath for example congestive heart failure, pulmonary hypertension, smoking, deconditioning etc. A review of patient's self-management skills should also be incorporated into the initial review and a written action plan, based on the review should be generated by the patient and the health care team. Spirometry should be done at least once per year.

Table 3: General COPD recommendations adapted from GOLD 2020.[1]

	mMRC 0-1, CAT<1.0	mMRC ≥0-1, CAT≥1.0
0-1 moderate exacerbation not needing hospitalization	Group A A bronchodilator (short or long acting)	Group B A long acting bronchodilator
≥2moderate exacerbations or ≥1 exacerbation needing hospitalization	Group C LAMA	Group D LAMA LAMA+LABA (if CAT>20) LABA+ICS (if EOS>300
long-acting muscarinic antagonist (LAMA),long-acting beta$_2$ agonist (LABA), inhaled corticosteroids (ICS), COPD assessment test (CAT), Modified Medical Research Council (mMRC), Eosinophils (EOS)		

Figure 5: Patient re-assessment and management at follow up visit in stable COPD

Having established an initial pharmacological regimen in a patient with stable COPD, during the follow up visit, the patient's response to pharmacological treatment will need to be evaluated. If the patient has responded appropriately to the prescribed agents and has no adverse effects, then the patient can remain on those medications. If the patient is not controlled upon review, then consideration must be given to which symptom should be the goal for future therapy-exacerbations or dyspnea. Also, the patient's compliance with inhalers and their techniques needs to be reassessed. Non-pharmacological interventions should also be reviewed to ensure that these are not contributing to the patient's lack of appropriate response to therapy. Having determined which symptom is to be targeted then the adjustment in treatment can be made.

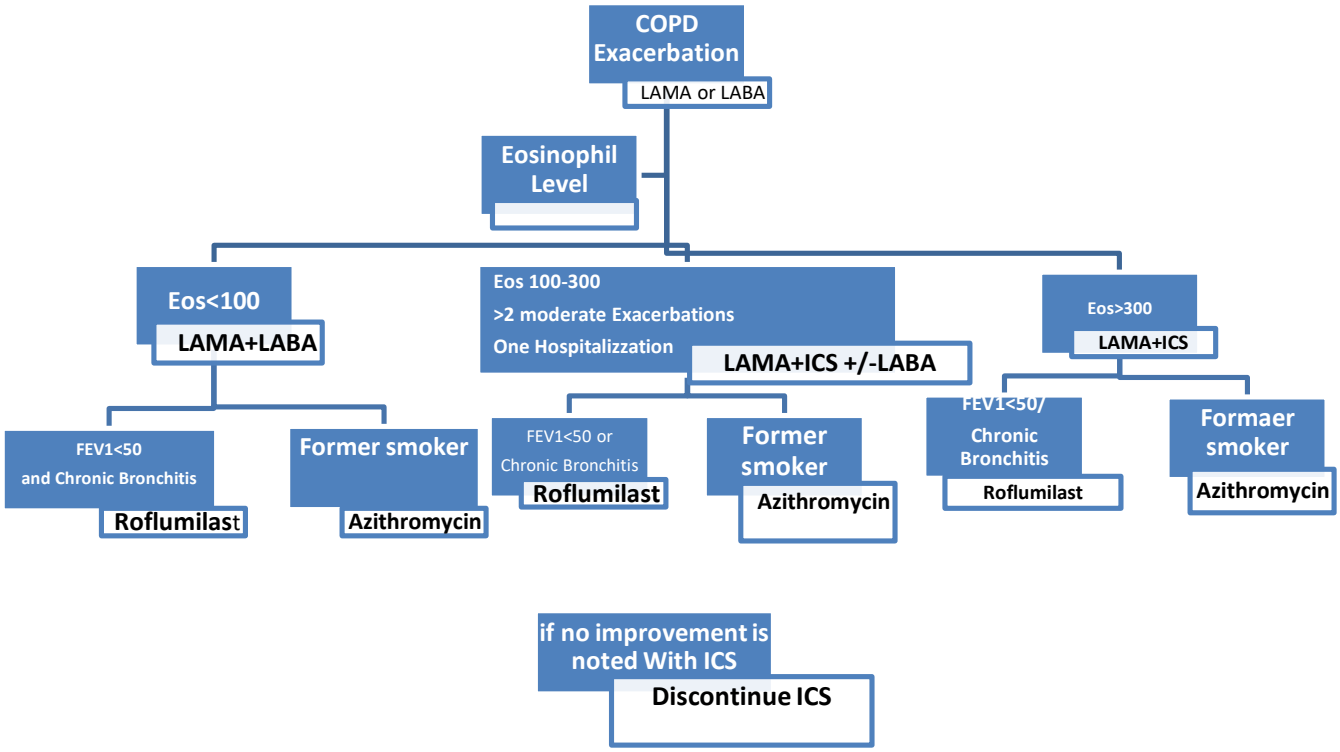
These adjustments do not take into consideration the patients GOLD ABCD categories that were made at the time of diagnosis.[1]

In patients in whom dyspnea or exercise limitation is the predominant symptom target, if they were on a LABA or LAMA

alone (monotherapy), then an escalation to both a LABA and LAMA can be done. Ensure that the device the patient is using for delivery is appropriate and the patient is using the inhaler as he/she should. It is prudent to also rule out other causes of dyspnea. LABA and an ICS or LABA, LAMA and ICS (triple therapy) can also be considered. It is prudent to de-escalate or stop the ICS once clinical goal is achieved, in the setting of lack of response, adverse reactions and or pneumonia occurs. Any treatment modification should be done under close medical supervision.[1,17]

In patients whose primary symptom target is to reduce exacerbations, who are already on a LABA or LAMA, monotherapy, they can be switched to a LABA and a LAMA.[1,10,17] If the eosinophil count is >300, [1,18] or they have had one hospitalization or eosinophil count is greater than 100 with more than 2 moderate exacerbations then consider a LABA and ICS. Patients can also be escalated to a LABA and LAMA and ICS if either the LABA and LAMA or LABA and ICS combinations are not working. Roflumilast is considered in patients with FEV1<50% a chronic bronchitis in whom the LABA and LAMA and ICS combination or the LABA and LAMA combination with a blood eosinophil count of less than 100, is not working. In former smokers, with blood eosinophils <100cells/ul, Azithromycin can be used if the ABA and LAMA and ICA combination is not working. It is recommended to de-escalate or stop where possible from ICS if appropriate clinical response is achieved, if there is no appropriate clinical response, there are adverse reactions or if pneumonia occurs.

The non-pharmacological management of stable COPD is discussed in detail in another section of this series.[19]



Management of COPD Exacerbations

COPD exacerbation is an acute worsening of respiratory symptoms that result in additional therapy. There are several factors that can precipitate COPD however the most common causes are respiratory tract viral infections such as human rhinovirus or the common cold. Exacerbations associated with viral infections are usually more severe, last longer and lead to hospitalizations. About 50% of COPD exacerbations are mild and are not reported. [19]/These unreported exacerbations, while shorter in duration, still have a considerable impact on the health status of the patient. The goal of care for the management of COPD exacerbation is to curtail the harmful effects of the present exacerbation and prevent subsequent events especially those that require hospital visits or hospitalizations. Patients who are admitted have an inpatient mortality of about 3-4%. [20] A patient with COPD exacerbation requiring ICU admission has a 43-46% risk of death within a year after hospitalization. The risk of death from an exacerbation increases with the development of respiratory acidosis, presence of comorbidities and the need for ventilatory support.

Whenever patients with COPD present with worsening dyspnea, the differential diagnosis for COPD should always be considered and their exclusion worked into the assessment of the patient.

Table 4: Differential diagnoses and the Assessments to consider in the setting of COPD exacerbation

CONDITION	PULMONARY EMBOLISM	PNEUMONIA	PLEURAL EFFUSION	PNUEMOTHORAX	PULMONARY EDEMA-CARDIAC	CARDIAC ARRHYTHMIAS - AFIB/AFLUTTER
ASSESSMENT	D-DIMER DOPPLER U/S OF LOWER EXTREMITIES CTPE PROTOCOL	CXR CRP PROCALCITONIN	CXR ULTRASOUND	CXR ULTRASOUND	CARDIAC ENZYMES EKG	EKG

Table 4: Criteria for hospitalization and admission to the ICU.[1,21] -In making this decision, local resources need to be considered

CRITERIA FOR HOSPITALIZATION	CRITERIA FOR ICU ADMISSION
1. Failure of outpatient therapy 2. Altered Mental Status-confusion/drowsiness 3. Hypoxia/Hypercarbia 4. Unable to take oral medication 5. Marked increase in shortness of breath 6. Not enough support at home 7. Serious comorbidities-heart failure etc	1. Marked lethargy/coma 2. Respiratory muscle fatigue 3 Impending respiratory failure/respiratory failure 4.Worsening hypoxemia 5.Marked confusion 6. Respiratory Acidosis pH<7.25 7. Hemodynamic instability-vasopressor use.

The management of exacerbations is based on whether the exacerbation is mild, moderate or severe.[1]

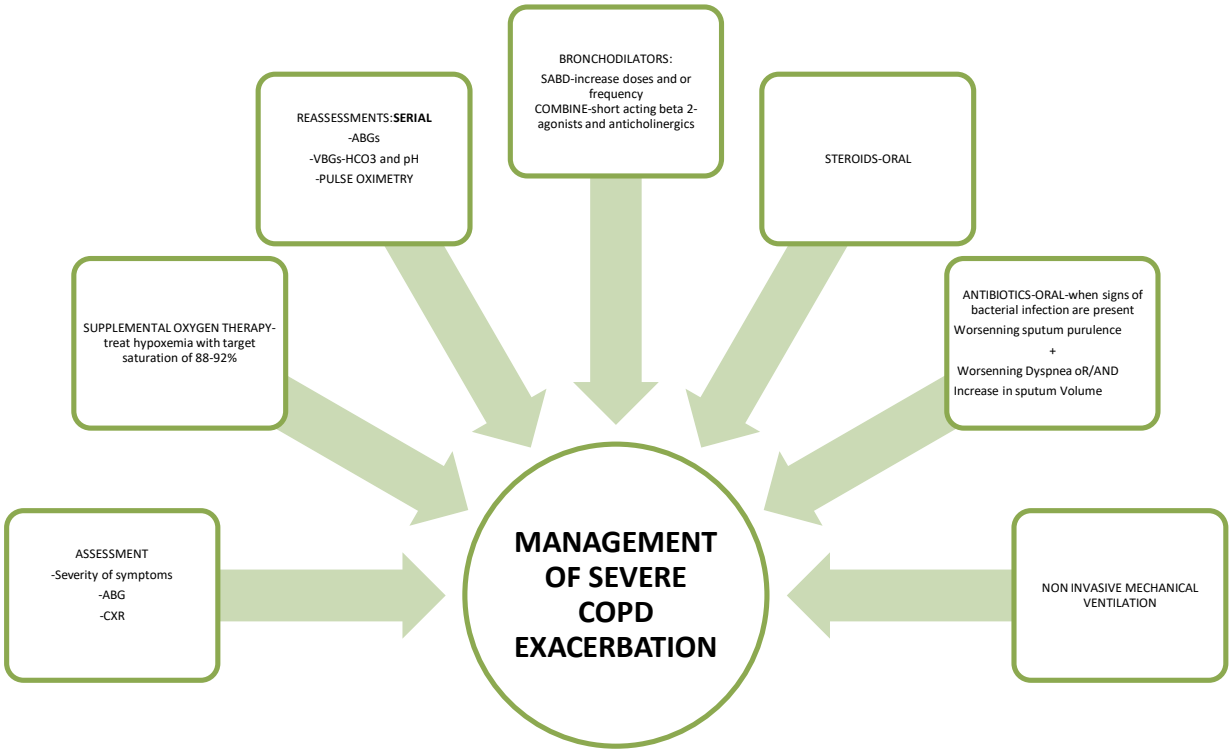
Mild exacerbation-SABA only
Moderate exacerbations- SABA+ antibiotics and or oral corticosteroids.
Severe exacerbations- ER visit or hospitalization-may be associated with acute respiratory failure.
Points to consider in the management of COPD exacerbations include:[1]

- In the setting of an acute COPD exacerbations inhaled SABA with or without SAMA is the first line therapy.
- Systemic glucocorticoids in COPD exacerbation, improves oxygenation and lung function, shortens the recovery time and hospital stay but should not be used for more than 5-7 days
- Methylxanthines have a narrow therapeutic index with dose related toxicity. The benefits gained from using methylxanthines occur at near toxic

doses. As such they are not recommended for use in this setting.

- Antibiotics, when indicated may reduce hospitalization duration, the risk of the patient relapsing early, treatment failure and can shorten recovery time. 5-7 days of therapy is recommended.
- For COPD patients with acute respiratory failure, the first method of ventilation should be non-invasive mechanical ventilation (NIMV), except contraindications. This method of ventilation has been shown to decrease the work of breathing and improve gas exchange thus decreasing the need for intubation, subsequently leading to decreased hospital stay and improved survival rates.
- SABA-inhaled with or without short acting anticholinergics are recommended for the initial treatment of an acute exacerbation regardless of severity.
- Systemic corticosteroids should be prescribed as it has been shown to improve oxygenation and lung function (FEV1) and shorten hospitalization duration and recovery time.
- Steroid use whether a short or long course, is associated with an increased risk of pneumonia, sepsis and mortality. As such their use should be limited to patients with severe exacerbations. When prescribed the duration of therapy should be 5-7 days.
- Antibiotics have been shown to decrease hospitalization duration, treatment failure and shorten recovery time while reducing the risk of early relapse. It is safe to determine antibiotic use based on the patient's sputum color as it has been found that sputum purulence is a good indicator for bacterial load.[1,22] In patients in whom antibiotics are indicated the duration of therapy should be 5-7 days.
- If COPD patients with exacerbation, progress to acute respiratory failure, high-flow nasal therapy (HFNT) is an option.

Figure 6: Management of severe COPD exacerbation not requiring ICU admission



Additionally, careful attention to the patient fluid balance and VTE prophylaxis using SQ heparin or LMWH should be carried out.

High-flow nasal therapy (HFNT)

HFNT delivers an air/oxygen blend that is humidified and heated via a nasal cannula. It delivers this mixture at up to 60 L/min of flow. It is considered to have several physiological effects that result in improved oxygenation, a reduction in intubation rate and clinical outcomes for patients with acute respiratory failure.[1,23] It does not however have any effect on mortality

The Effects of High Flow Nasal Therapy

- Decrease respiratory rate/effort to decrease work of breathing
- Decrease anatomical dead space-improved lung volume
- Decrease peep effect
- Improves gas exchange
- Improves dynamic compliance, trans pulmonary pressures and homogeneity

Figure 7: Indications for the use of Invasive Mechanical Ventilation in patients with COPD exacerbation

Factors that are associated with poor outcome in patients with COPD include:

1. Previous hospitalizations for COPD exacerbation: It has been shown that the long-term prognosis after hospitalization for COPD exacerbation is poor.[24-26] There is a 5-year mortality rate of 50 %.
2. The presence of comorbidities- cardiovascular disease/lung cancer
3. Older age
4. Low BMI
5. The degree of severity of the index exacerbation
6. The need for home oxygen upon discharge
7. Mortality risk may be amplified during cold weather

Factors associated with increased mortality following an acute COPD exacerbation:

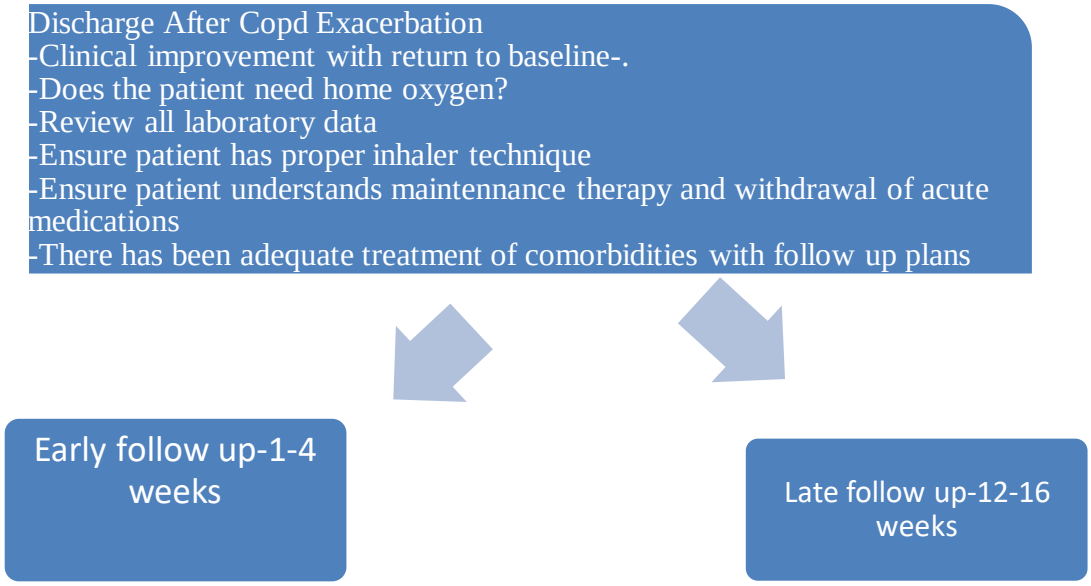
- Higher prevalence and severity of respiratory symptoms
- Lower exercise capacity

- Lower lung density
- Thickened bronchial walls on CT-scan
- Poorer quality of life
- Worse lung function

As a part of the action plan for acute exacerbation, patient education should be reinforced particularly with respect to the use of steroids and antibiotics. This has been shown to reduce hospitalizations.

The duration of hospitalization culminates with the decision to discharge.[1,27] Part of reducing relapses and exacerbations upon discharge rests in ensuring that the patient has met the criteria to be discharged and has appropriate follow up.

Figure 8: Hospital discharge after COPD exacerbation

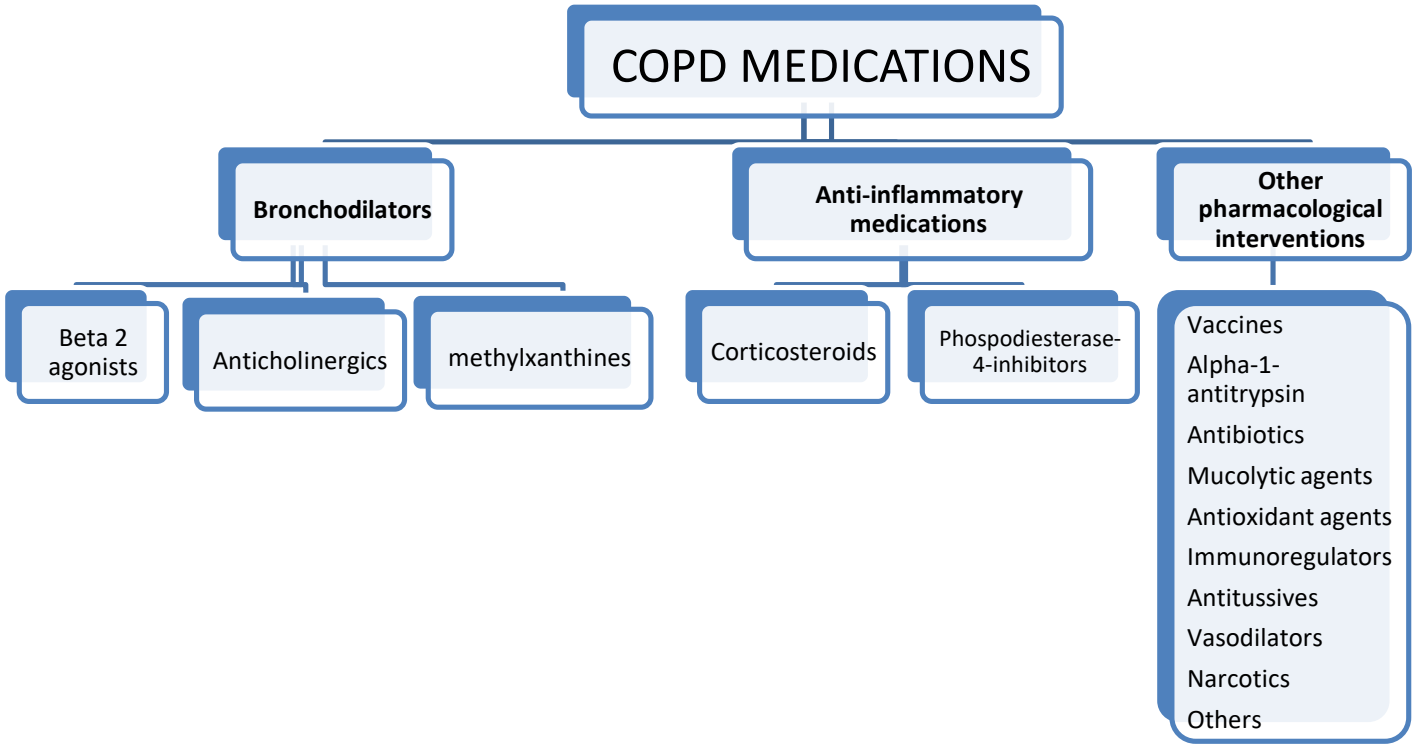


Follow up is key in preventing future exacerbations. At these visits, patients should be evaluated for their capability to manage in their typical environment and their capacity to carry out their ADLS as well as to do physical activity should be noted. Symptom documentation using CAT or mMRC should be done and the treatment regimen should be reviewed and the patients understanding and compliance should be assessed. Inhaler technique and the need for long term oxygen should be evaluated. The status of comorbidities should also be determined. At the 12-16-week visit, spirometry to evaluate FEV1 is recommended.[1]

Figure 9: Interventions that decrease the frequency of COPD exacerbations.[28-31]Pharmacological interventions are aimed at prevention or reduction of symptoms and exacerbations while improving the patient's health status and exercise tolerance. These interventions do not change the natural

progression of the disease and lung function still declines over time. There are several classes of medications available for treatment of COPD. The choice of medication is based on the individual patient's disease stage, severity of exacerbations, the patient's ability to manipulate devices (Metered Dose Inhalers-MDIs vs Breath Activated or Spacer Devices vs Dry Powder Inhalers-DPI) for delivery of medications, cost effectiveness and the patients' response to the medication.[2] The success of the pharmacological therapy is based on decrease or resolution of symptoms and not on changes in lung function as the disease is expected to remain at baseline or progressively worsen.

Figure 10: Medications for COPD

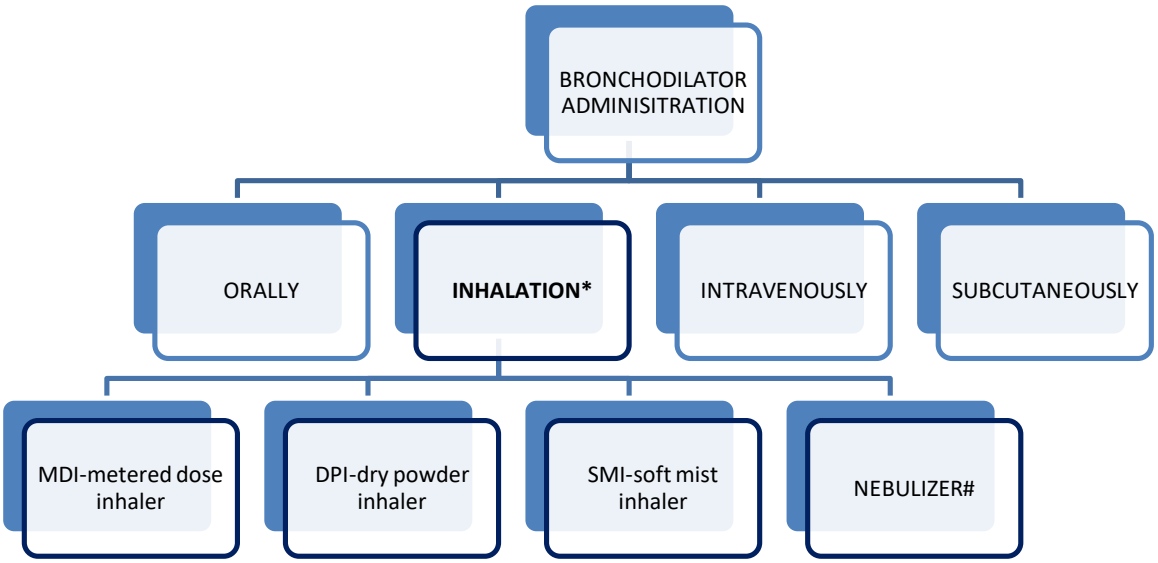


Bronchodilators: beta 2 agonists/ anticholinergics/methylxanthines

Bronchodilators are the foundation drugs for the management of patients with COPD.[1,15,32,33] They are used to reduce or

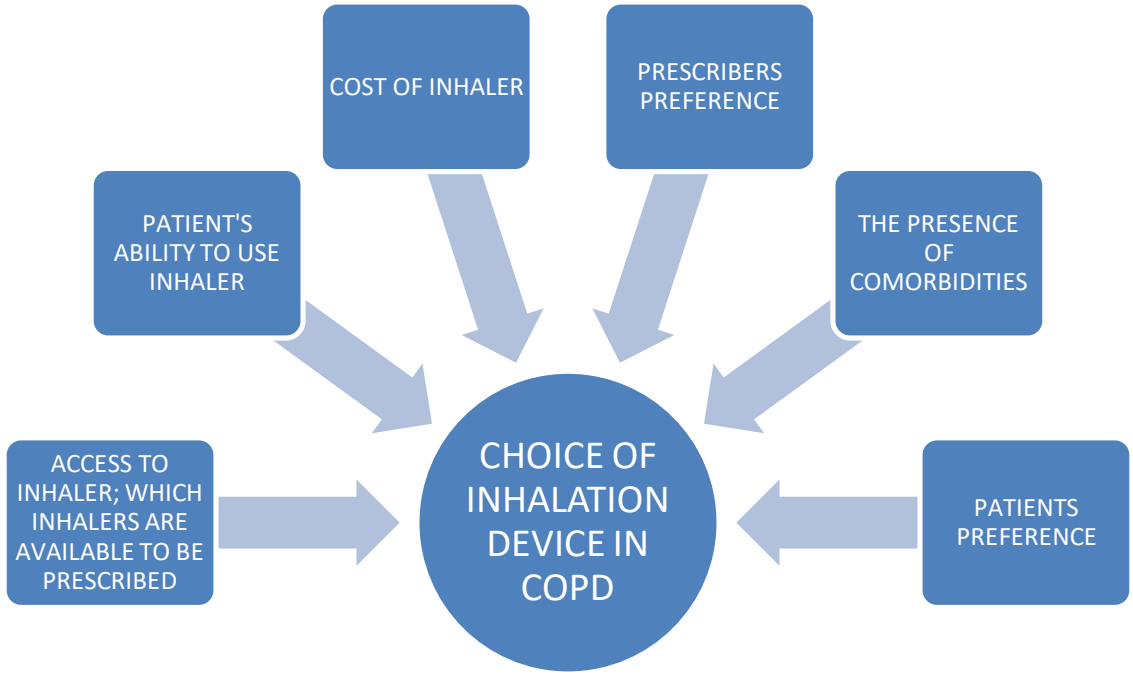
prevent symptoms but are not recommended for use on a regular basis. They work by changing the tone of the airway muscles, thus increasing the diameter of the airway. The hyper inflated lungs are then able to empty better. They increase the FEV1. Drugs in this category include beta agonists, anticholinergics and theophylline. Bronchodilators studies have shown that these agents cause symptomatic relief, but do not offer any spirometric improvement. With bronchodilators, patients experience improved exercise capacity and long term improvement in their symptoms. Bronchodilators can be given on a schedule to prevent or reduce exacerbations or as needed to treat acute symptoms. Bronchodilators may be administered by inhalation, orally or parenterally depending on the drug administration routs available. In COPD, inhalation is the method of choice as it enhances the direct effect of the bronchodilator on the airway whilst limiting the systemic effect. Inhalation may be by several methods as noted on figure 11.

Figure 11: Bronchodilator Administration:



*Inhalation is the method of choice. To ensure the effectiveness of the drug given by this route, correct inhaler technique should be ensured and patient education should be geared towards optimizing when and how to use their inhalers. The type of inhaler prescribed should be individualized based on the patient's ability to use the inhaler, the presence of comorbidities, the cost of the inhaler and what inhaler is available to be prescribed.

Figure 12: The choice of inhaler device in patients with COPD



There is no strong evidence to show that nebulizer administration of bronchodilators confer any benefit over other methods of inhalation. Patients do however report symptomatic relief with nebulizers in the acute setting not achieved with other inhalation methods. If a nebulizer is used in acute COPD exacerbation, then air-driven nebulization is the preferred method. It is noted that oxygen driven bronchodilator nebulization puts the patient at risk for possibly retaining CO2 leading to increase in the PaCO2. The handheld inhalers are cheaper, simpler and easier to carry than nebulizers which even at their most streamline are bulky.

The beta agonists and anticholinergics may be long or short acting. The long acting bronchodilators are the drug of choice for producing long term symptomatic relief compared to short acting agents. Bronchodilators may be used singly or in combination. There are several formulations of this agent from which to choose.

Table 6: Long acting beta 2 agonists (LABA)

Beta 2 agonists

These agents stimulate the beta 2 adrenergic receptors, releasing cyclic AMP resulting in relaxation of airway smooth muscle and thus bronchodilation. Patients feel subjectively better and their FEV1 increases. There are long acting beta 2 agonists (LABA) and short acting beta 2 agonists, (SABA). The SABAs swear off in about four to six hours and LABAs last for more than twelve hours. The SABAs are prescribed as rescue agents and regularly scheduled use is discouraged as there is an increase in adverse side effects without much improvement in lung function exercise capacity or symptoms.[1]

Long acting beta 2 agonists: positive profile	Long acting beta 2 agonists: negative profile
• Reduce the risk of exacerbations • Reduce hospitalizations although not consistently • Improve respiratory health status • Improve FEV1 and lung volumes • Improve dyspnea • Improve quality of life	• Have no effect on mortality rate. • Do not stop the rate of decline of lung function • Dry mouth • Urinary retention • Hypersensitivity reactions • Symptoms of narrow angle glaucoma • Dizziness • Headache • Tremor • Throat irritation

Examples of LABA include formoterol and salmeterol which are taken twice daily and indacaterol, oladaterol and vilanterol which are once a day formulation.[34] Side effects of short acting beta 2 adrenergic agonists include palpitations, tremor, hypersensitivity reaction and tachycardia. Additionally pulmonary vasodilation can worsen ventilation-perfusion matching resulting in a slight fall in arterial PaO2.

Anticholinergics-Antimuscarinics

Broncho-motor tone is mostly regulated by the parasympathetic nervous system. Actions in the nervous system are facilitated through nicotinic (N) and muscarinic (M) receptors via the neurotransmitter acetylcholine (Ach). Release of Ach, to act on these receptors, results in bronchoconstriction. These drugs block the acetylcholine effect on muscarinic receptors. There are several muscarinic receptors M1-M5. Anti-muscarinic drugs, used in COPD, block the bronchoconstriction effect on the M3 muscarinic receptors in the smooth muscle of airways. Short acting anticholinergics (SAMA) for example oxitropium and ipratropium also block M2 receptors (inhibitory receptors that can potentially cause bronchoconstriction which is vagally induced). Long acting anticholinergics (LAMA) for example tiotropium and umeclidinium bind to the M3 muscarinic receptors for a protracted period and separates from the M2 receptors faster. This causes the bronchodilator effect to be of a longer duration.[1,33] LAMAs have been shown to reduce the frequency of exacerbations and subsequent hospitalization (more so than LABAs), improve symptoms and health status as well as improve the success of pulmonary rehabilitation. The quaternary compounds of this group of agents is used for the treatment of COPD as they are poorly absorbed after oral administration and causes fewer side effects as compared to tertiary compounds such as atropine. There is no appreciable CNS effect. Additionally, as they are poorly absorbed from the lungs, they do not inhibit mucociliary clearance so there is no increased accumulation of lower airway secretions. Poor absorption from the gastrointestinal tract as well as the lung results in little or no change in BP, intraocular pressure and bladder function. The short acting anticholinergics such as ipratropium

bromide are preferred over beta-2 agonists and methylxanthines. They are more effective it is more effective and as compared to beta agonist the cardiac stimulatory effect is minimal. Treatment with anticholinergics results in improvement in exercise tolerance, relief of dyspnea and improvement in quality of life. Treatment does not however change the natural course of the disease as it does not have anti-inflammatory properties and so there is no need to use in asymptomatic patients. The duration of action of these short acting agents is about 6-9 hours. Ipratropium bromide can be used alone or in combination therapy. It can be delivered by MDI as well as nebulized solution. It has been shown by several studies to be superior to beta-adrenergic agonists because of is minimal side effects compared to its beneficial effects. In combination with beta agonists, the benefits are optimized as there is more bronchodilation achieved compared to the administration of single agents alone. They can be given together, in immediate sequence or separated by an interval as there are no studies to show as yet any benefits of one method over the other. Another short acting anticholinergic is oxitropium bromide and is available as an inhaler and a solution for nebulizer.[33,35]

Table 7: Benefits of combination short acting bronchodilators. [33,35]

Benefits of using Ipratropium and beta agonists together
Both classes of medication, by different mechanisms, result in bronchodilation.
By giving both drugs together there is a rapid onset of action by the beta agonists and a long term effect due to the activity of the anticholinergic agents.
Beta agonists act on the distal small airways and anticholinergics act mostly on the proximal large airways, thus the entire lungs are affected.

Long acting anticholinergic agents

These drugs include tiotropium, aclidinium, umeclidineum and glycopyrronium.[1,33] The most commonly used anticholinergic agent to date, is tiotropium. Tiotropium is well tolerated and is associated with:

- A reduction in hyperinflation
- Decreased shortness of breath
- Less acute exacerbations of COPD
- Reduced hospitalizations as a result of exacerbations
- Improves lung function
- Improves quality of life

Table 8: Long acting anticholinergics [33,35-37]

DRUGS	MAIN RECEPTORS INHIBITED	DURATION OF ACTION	MODES OF ADMINISTRATION
Tiotropium	M1, M3, uncouples from the M2 receptors rapidly.	24hrs	Dry powder inhaler/ Soft mist inhaler

Umeclidinium	Mainly at M3	24hrs	Dry powder inhaler
Aclidinium	Selective at M3	12hrs	Dry powder inhaler
Glycopyrronium	M1 M3 more so than M2	24hrs	Dry powder inhaler

Potential risks and side effects of long acting anticholinergics.[1,33,37]

The side effect profile of anticholinergic agents is safe, mainly due to their poor absorption from the mouth and gastrointestinal tract. The main side effect in this class of drugs is dry mouth. Tiotropium as a soft mist inhaler has been shown in one study to cause an increased risk of mortality compared to placebo. However another study contradicted this. Aclidinium has been associated most commonly with cough, headache and nasopharyngitis as well as the other anticholinergic side effects of constipation, urinary retention and dry mouth. Glycopyrronium's most common side effects were dry mouth and urinary tract infection [1,33].

Methylxanthines

Theophylline is the most commonly used drug in this class.[1,5] It is not clear exactly how Methylxanthines work, as they are reported to have a wide range of non-bronchodilator effects. The main idea is that they work as nonselective phosphodiesterase inhibitors.

Use of theophylline has been shown to cause a moderate bronchodilator effect. It is metabolized by cytochrome P450 mixed function oxidases. Low doses of theophylline causes a reduction in exacerbations but does not improve post-bronchodilator lung function. Clearance of the drug decreases with age and other drugs and physiologic conditions alter the metabolism of these drugs.

Theophylline has a narrow therapeutic ratio and its adverse effects are dose-related. To achieve maximum effect, the dose of theophylline needed would be toxic. Because they are nonselective phosphodiesterase inhibitors, they have a wide range of toxic effects.

Side effects of methylxanthines

- Cardiac arrhythmias
- Grand mal convulsions
- Headaches
- Insomnia
- Nausea
- Heart burn
- Interactions with frequently used medications: Coumadin
- Overdose

Combination of bronchodilators

Bronchodilators with different duration of action and mechanism of action maybe combined. This may result in an increase of bronchodilation while maintaining the same side effect profile or less so.[38] Summarily, when combining bronchodilators, the following are some points to remember:

1. Combining a SABA and SAMA leads to a better outcome with respect to improving both symptoms and the FEV1, than using either medication alone.
2. Combination of a LABA and LAMA is superior to treatment with either medication alone. This combination improves

breathlessness, quality of life, reduces exacerbation rates, hospitalizations and improves lung function-increases FEV1.

- Anti-inflammatory Agents:
  Anti-inflammatory agents available for the treatment of COPD include:
- Inhaled corticosteroids
- Oral glucocorticoids
- Phosphodiesterase inhibitors (PDE4)
- Antibiotics
- Antioxidant agents
- Mucoregulators

Note that leukotriene modifiers have not been approved for use in COPD as they have not been studied in this population. The efficacy of anti-inflammatory agents is based on the exacerbation profile of the patient, for example the time to first exacerbation and the rate of exacerbations.

Steroids

Inhaled and systemic steroids are widely used in the treatment of COPD.[1,35] The rationale for doing so is the belief that COPD is an inflammatory condition involving primarily the lung but may be systemic also. There are however controversies surrounding this belief and while the role of steroids in asthma has be proven by several studies, there are no clear studies that this is the case with COPD. Currently the use of steroids in the management of stable COPD is restricted to specific indications, while its use in COPD exacerbation has been demonstrated to have marked beneficial effects on the course of the illness.[16,33,36,37,39]

Table 9: Inhaled corticosteroids (ICS) and Systemic Corticosteroids

INHALED CORTICOSTEROIDS	SYSTEMIC CORTICOSTEROIDS
The dose response relationship is unknown	Limited for use in patients with acute exacerbations.
The long term safety is unknown	Beneficial in patients hospitalized for acute exacerbation of COPD
Regular treatment reduces exacerbations	The beneficial dose and duration of treatment are not clearly defined.
Regular treatment improves quality of life, lung function and symptoms.	Oral and IV steroids have been found to be equally effective in preventing treatment failure
Does not change mortality in patients with COPD	Hasten recovery in acute exacerbations. Reduces rate of relapse, improves lung function and dyspnea and reduces the rate of treatment failure.
Do not change the long term fall in FEV1	There is no study currently to support the use in patients with stable COPD
Side effects: * increased risk of pneumonia, oral candida, hoarseness, skin bruising	Side effects: infection, hypertension, osteoporosis, weight gain, adrenal suppression, cataracts, glucose intolerance, GI discomfort, steroid myopathy.

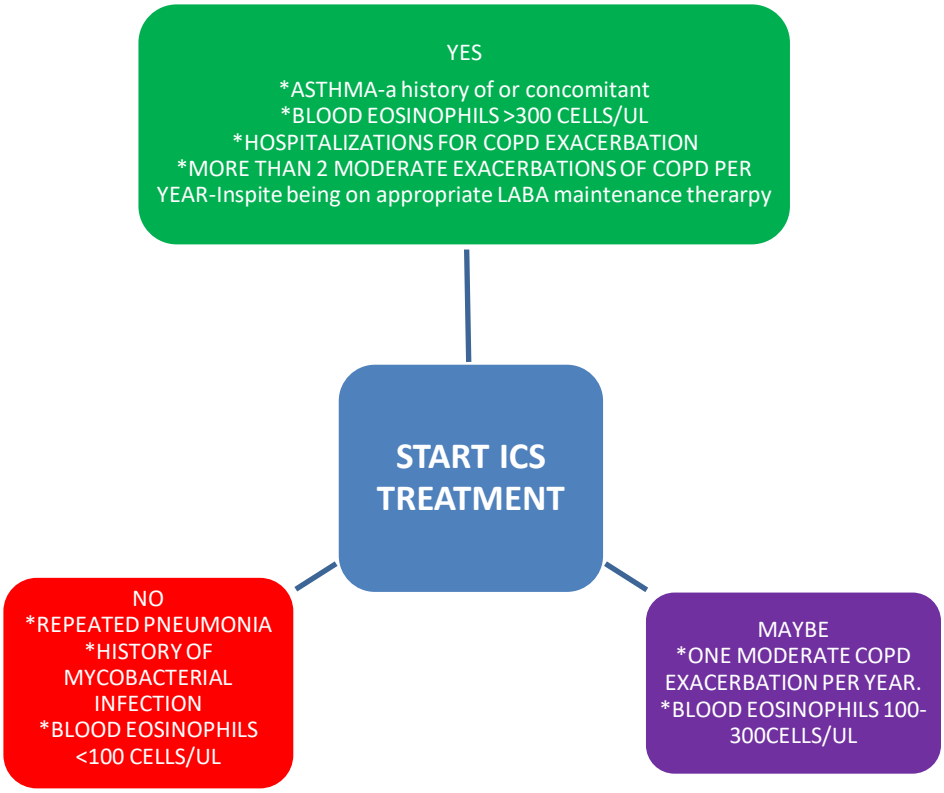
* Increased risk of pneumonia is seen in patients older than 55 years with a BMI<25kg/m2, still smoking, have had pneumonia before, a poor MRC score and or severe airflow limitation and frequent exacerbations.

Notes:

1. Inhaled corticosteroids (ICS) used regularly in patients with COPD, does not impact the overall decline of FEV1 nor does it affect mortality.
2. The risk of pneumonia is increased with the regular use of ICS, primarily in those with severe COPD.
3. ICS + LABA improve lung function, reduce exacerbations and improve lung function than either drug alone, more so in patients with moderate to very severe COPD and exacerbations.
4. Triple inhaled therapy- ICS+LAMA+LABA: This combination has been shown to be superior to ICS+LABA, LAMA or LABA+LAMA in improving lung function, preventing exacerbations and improving symptoms and patient reported outcomes. There are also trials showing reduction in the mortality rate in patients with severe and or frequent exacerbations with lots of respiratory symptoms.[1,40,41] If withdrawal of steroids is being considered after stabilization in patients with COPD, it should be done with great caution even though studies done to date have been equivocal. Some studies have shown increased exacerbations and or symptoms after stopping ICS while other studies have not demonstrated this. It is thus prudent to be very cautious when withdrawing ICS after use.

When considering starting ICS, there are several factors to consider as noted in Figure 13.

Figure 13: Factors to consider when starting ICS therapy.



7.3.3 Other pharmacological therapies:

Other pharmacological therapies worth mentioning include:

- Phosphodiesterase 4 inhibitors: (PDE4) Inhibitors: These drugs reduce inflammation by stopping the breakdown of intracellular cyclic AMP. An example is Roflumilast. Roflumilast has no direct bronchodilator properties and is a once a day formulation. It has shown efficacy in patients with severe to very severe COPD, a history of exacerbations and chronic bronchitis being treated with systemic corticosteroids. It reduces exacerbation and improves lung function in patients on fixed-dose ICS+LABA combinations. The beneficial effects of roflumilast is reportedly greater in COPD patients with a history of hospitalization due to acute exacerbation. Comparative studies with an ICS are not available. Adverse effects include, nausea, anorexia, diarrhea, weight loss, abdominal pain, headaches and sleep abnormalities. It is recommended to be used with caution in patients with depression.
- Mucolytics -Regular treatments with mucolytics for example NAC, can improve symptoms and reduce exacerbation in COPD patients not on ICS.
- Antibiotics-Regular use of azithromycin and erythromycin may reduce exacerbation rates. Dosages of -Azithromycin 250mg/day or 500mg three times per week or Erythromycin 500mg twice daily-for one-year decrease

exacerbations compared to customary care. Side effects with azithromycin include increased bacterial resistance, prolongation of the QTc interval and abnormal hearing tests.

- Immunoregulators-Various studies have shown a decrease in the frequency and severity of COPD exacerbations however the effects have not been reproducible and varied between studies and doses. Additionally, there is no effect on FEV1, health status and the peripheral blood eosinophil count and response to treatment. More studies regarding the use of these agents in the treatment of COPD is needed.
- Vaccines-Influenza and pneumonia vaccines have been shown to reduce morbidity and mortality in patients with COPD. In patients age <65 with an FEV1<40% predicted and with comorbidities, the 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been shown to decrease the incidence of community acquired pneumonia. The 13-valent conjugated pneumococcal polysaccharide vaccine (PCV13) has been shown to decrease serious invasive pneumococcal disease and bacteremia.
- Antitussives-To date, there is no evidence that using antitussives in patients with COPD is beneficial.
- Others-Vasodilators may worsen oxygenation and does not improve outcomes in patients with COPD. IV augmentation therapy with alpha 1 antitrypsin may slow the progression of emphysema.

Conclusion

COPD management is still a work in progress despite all the advancements in treatment and ongoing research. COPD management is a multidisciplinary team effort. The decision to start treatment is based on the level of symptoms and the risk for exacerbations. Treatment is adjusted based on whether the patient continues to have exacerbations while on maintenance therapy and if the symptoms of breathlessness or exercise limitations are present. Patient education also plays an integral part in the management of stable COPD.

Management of COPD starts with an early diagnosis, a thorough history with attention to exposures to risk factors.[1,2,5] Decrease exposure to air pollutants and occupational dusts and chemicals pollutants should be a priority. Tobacco cessation is indispensable in the management of COPD. COPD Management is a step wise process that starts with patient education, aggressive risk factor managements, and then pharma-cological management starting with Bronchodilators-scheduled/PRN, Inhaled steroids-used in patients with symptomatic COPD with spirometry response to steroids or FEV1 <50% predicted and repeat exacerbations that need antibiotics and oral steroids . Exercise Training improves exercise tolerance and decreases both dyspnea and fatigue while Long term oxygen therapy, (>15L/d) in patients with chronic respiratory failure decreases mortality. [5] Identify the exacerbating factors like infection or air pollution and treat, eliminate or reduce accordingly. A third of COPD exacerbations

have no identifiable cause. Pharmacological management focuses on the treatment of symptoms, maintaining asymptomatic stable states and reducing exacerbations.

Previous hospitalizations for COPD exacerbation are associated with poor prognosis. Other factors associated with poor prognosis include the presence of comorbidities-cardiovascular disease/lung cancer, old age, a low BMI, the need for home O2 and the degree of severity of the index exacerbation.

Mortality risk may be amplified during cold weather. Higher prevalence and severity of respiratory symptoms, lower exercise capacity, lower lung density, poorer quality of life worse lung function and thickened bronchial walls on CT-scan are highly associated with increased mortality in patients with COPD. Pharmacological management has not been shown to reverse or cure COPD. The future goal should be to treat COPD with pharmacological management. So far, lung transplant is the only known curative treatment for COPD. Criteria for surgical management are restrictive and the risks associated with surgery are still very high. A multidisciplinary team effort with pharmacological management at the center may be most realistic hope for a more inclusive treatment focusing on the cure for patients with COPD.

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