



Update on management of stable chronic obstructive pulmonary disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is a major chronic debilitating condition with significant impact on quality of life, symptoms, comorbidity, health care utilization and longevity. The main pathophysiological hallmark of COPD is expiratory flow limitation which impairs the ability of respiratory system to adequately and properly ventilate. To be able to prognosticate and manage patients with COPD, various societies have developed classifications of disease severity. Current classification schemes combine three elements that include lung function, patient reported symptoms (shortness of breath) and frequency of exacerbations. Global Initiative for Obstructive Lung Disease (GOLD), an international guideline for diagnosis and management of COPD, started using this approach since the 2011 revision. Management according to this scheme has been developed and is in use. Comprehensive COPD management is multifaceted. It includes pharmacologic management, patient education, smoking cessation, influenza and pneumococcal vaccinations, depression and anxiety management, pulmonary rehabilitation, and if indicated, home oxygen therapy. The following chapter will review management recommendations currently in use for stable COPD. We intend to make the chapter to the point and practical and avoid an exhaustive review of the literature.

Keywords: Pharmacotherapy; bronchodilator; disease management

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major chronic debilitating condition with significant impact on quality of life, symptoms, comorbidity, health care utilization and longevity. Clinically, COPD is characterized by gradual development of shortness of breath, cough, sputum production, and repeated episodes of acute worsening of respiratory status called COPD exacerbation. Cigarette smoking is the main cause of COPD. The main pathophysiological hallmark of COPD is expiratory flow limitation which impairs the ability of the respiratory

system to adequately and properly ventilate. The expiratory flow limitation is caused by loss of elastic recoil support provided by alveolar attachments around the small airways, by inflammation and scarring of small airway walls, and by accumulation of mucus in the lumen of small airways. In addition, destruction of the lung parenchyma impairs the lung's ability to participate in gas exchange. Chronic inflammation is the main cause of changes seen in COPD (1).

To be able to prognosticate and manage patients with COPD, various societies have developed classifications of disease severity. Although initial classifications revolved around objective measures of lung function, practitioners

very soon recognized that patients with similar lung function impairments report various degrees of functional and subjective limitations. The newer classification scheme combines three elements that include lung function, patient reported symptoms (shortness of breath) and frequency of exacerbations. Global Initiative for Obstructive Lung Disease (GOLD), an international guideline for diagnosis and management of COPD, started using this approach since the 2011 revision (2). Management according to this scheme has been developed and is in use. Comprehensive COPD management is multifaceted. It includes pharmacologic management, patient education, smoking cessation, influenza and pneumococcal vaccination, depression and anxiety management, pulmonary rehabilitation, and if indicated, home oxygen therapy (1). The following chapter will review management recommendations currently in use for stable COPD.

Smoking cessation

Tobacco smoking is the main cause of COPD. Smoking cessation has the greatest capacity among all intervention modalities to influence the natural history of COPD. However, smoking cessation is not easy and on average, a smoker may try to quit several times before succeeding. Overall, the long-term tobacco cessation success rate is about 25% (3). The success rate has been shown to improve with implementation of smoking bans in addition to individual smoking cessation attempts (4).

Pharmacotherapies and non-pharmacotherapies for the smoking cessation

Nicotine replacement therapies such as nicotine gum, inhaler, transdermal patch, lozenge, sublingual tablet and nasal spray can increase smoking cessation success rates compared with placebo (5). The contraindications to nicotine replacement therapy are recent myocardial ischemia or stroke. Although controversial, it is suggested that after an acute coronary syndrome, nicotine replacement be started 2 weeks or later from the event onset (6,7).

E-cigarettes as smoking cessation agents are controversial despite their increasing use in this setting (7-11). Additionally, their overall safety has not been established and some organizations advocate for caution about their usage due to the paucity of safety data. Recent data suggest that these agents alter lung host response in smokers (12,13).

Other pharmacologic products such as varenicline,

bupropion and nortriptyline have been shown to increase the smoking cessation rate; however, they are best used as part of a supportive care component in smoking cessation to improve the cessation outcome (14-16).

The 5-step intervention program to include ASK, ADVISE, ASSESS, ASSIST and ARRANGE provides a reasonable strategy for providers helping patients quit smoking (5). As tobacco addiction is a chronic condition, the relapse rate is high and the providers should be aware of this without blaming either themselves or the patient for the relapse.

It is noteworthy that counseling provided by any of the healthcare professionals including a brief 3-minute session significantly increases the quit rate (17). It has also been shown that counseling intensity increases the quit rate success (18). Overall, counseling support has been shown to improve the tobacco cessation success rate at 6 months compared with the usual care (19). The combination of behavioral and counseling support in addition to pharmacotherapy has also been shown to improve the quit rate further (20).

Vaccination

Influenza vaccination reduces hospitalization due to lower respiratory tract infections leading to hospitalization and death in patients with COPD (21-24). Additionally, despite the paucity of studies evaluating COPD exacerbations, there appears to be evidence of significant reduction in the number of exacerbations in vaccinated COPD patients compared with those who received placebo (21). Vaccination with either live attenuated or killed virus is recommended as they are both effective in the elderly COPD patients (25). Additionally, a population-based study suggests that COPD patients and particularly elderly ones had a reduction in the risk of ischemic heart disease in influenza vaccinated patients and when these events occurred they were generally milder and more transient (26).

Pneumococcal vaccination with Pneumococcal Vaccine 13 (PCV13) and Pneumococcal Polysaccharide Vaccine 23 (PPSV23) are both recommended for all patients ages 65 or older. However, the PPSV23 is recommended for most younger COPD patients with significant chronic lung and/or chronic heart disease (27). Of note, specific recommendations regarding the efficacy of PCV13 and PPSV23 are limited and contradictory (28). Overall, the vaccination has been shown to reduce the risk of COPD exacerbation and therefore it is recommended in COPD

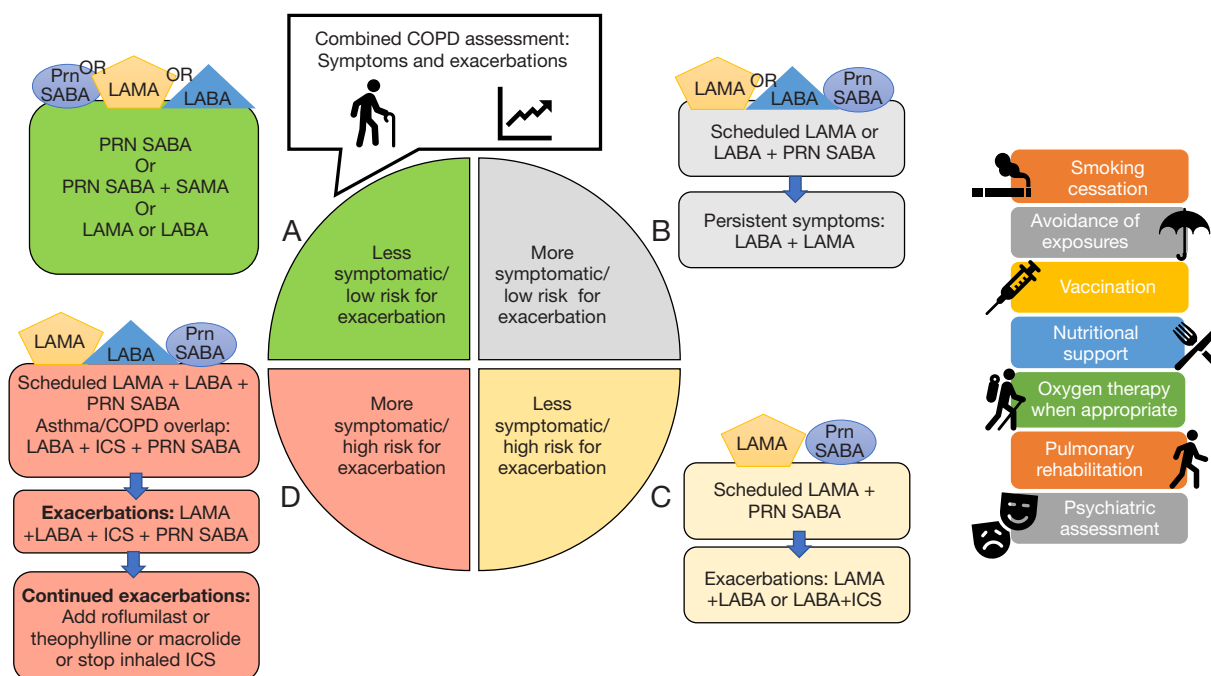


Figure 1 Management of stable COPD. SABA, short-acting bronchodilator agonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2 agonist; SAMA, short-acting muscarinic agonist; PRN, pro re nata; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

patients with a moderate quality of evidence. However, evidence comparing which type of vaccine is best in these patients was insufficient (29). The incidence of community acquired pneumonia was reduced in severe COPD patients younger than 65 with an FEV1 <40% of predicted and in those with cardiac comorbidities who received the PPSV23 vaccine (30). The PCV13 also has been shown to induce at least the same or higher immunogenicity of the PPSV23 vaccine in COPD patients for up to 2 years after the vaccination (31). Additionally, a large randomized controlled trial 1 has shown that the PCV13 vaccine had a significant efficacy for the prevention vaccine-type community-acquired pneumonia (45.6%) and vaccine-type invasive pneumococcal disease (75%) among adults age 65 or older and this efficacy lasted for at least 4 years (1,32).

In summary, yearly influenza vaccination is recommended for all stable COPD patients (Evidence B). The pneumococcal PPSV23 is recommended in younger patients with COPD and FEV1 than 40% of predicted (Evidence B). The pneumococcal PCV13 vaccination is recommended in all patients 65 and older as the evidence has shown that it reduces the risk of bacteremia and serious invasive pneumococcal disease (Evidence B).

Pharmacotherapy of stable COPD

The general principles of pharmacotherapy in COPD are initiation of medications based on individual patient phenotype and GOLD stratification with the three main goals of (I) alleviation of symptoms, (II) reduction in future complications including acute exacerbations of COPD and (III) improvement in exercise tolerance and quality of health (1). These medications are further classified into inhaled monotherapy, inhaled combination therapy, and systemic treatments (see *Figure 1* and *Tables 1-3*)

Bronchodilators

Bronchodilators, medications that relieve bronchial obstruction through airway smooth muscle relaxation, are the cornerstone of therapy in COPD. They have been shown to reduce air trapping both at rest and during exercise (1,44). Bronchodilators can be classified into two major groups based on their mechanism of action, β_2 -agonists and muscarinic receptor (M1, M2, and M3) antagonists. Within β_2 agonists and muscarinic receptor antagonists, there are both short acting (short-acting β_2

Table 1 Inhaled bronchodilators

Class of medication	Available medications	Benefits when compared to placebo	Adverse effects
SABA and SAMA (33,34)	Albuterol	Improves symptoms	SABA: Headache, tachycardia, tremors, hypokalemia
	Levalbuterol	Improves FEV1	SAMA: Dry mouth, Nausea, metallic taste, urinary retention
	Ipratropium		
	Albuterol/ipratropium		
LABA (35)	Indacaterol	Improves FEV1	Same as SABA
	Salmeterol	Reduces SGRQ	
	Olodaterol	Reduces AE	
LAMA (36,37)	Umeclidinium	Improves FEV1	Same as SAMA
	Glycopyrrolate	Reduces SGRQ	
	Tiotropium	Reduces AE	
	Acclidinium		

SABA, short-acting bronchodilator agonist; SAMA, short-acting muscarinic agonist; FEV1, forced expiratory volume in 1 second; LABA, long-acting β_2 agonist; SGRQ, St. George Respiratory Questionnaire score; AE, acute exacerbation risk reduction; LAMA, long-acting muscarinic antagonist.

Table 2 Inhaled combination therapy

Class of medication	Available medications	Benefits when compared to placebo	Benefits when compared to other medication	Adverse effects
LABA and LAMA combination (38,39)	Glycopyrrolate and formoterol	Improves FEV1	Compared to both LABA and LAMA individually:	Same as mono-components
	Indacaterol and glycopyrrolate	Reduces SGRQ	Improves FEV1	
	Olodaterol and tiotropium	Reduces AE	Reduces SGRQ	
	Umeclidinium and vilanterol		Reduces AE	
LABA and ICS combination (40)	Budesonide and formoterol	Improves FEV1	Compared to LABA/ICS combination:	Pneumonia
	Fluticasone propionate and salmeterol	Reduces SGRQ	Less improvement FEV1	Oropharyngeal candidiasis
	Fluticasone furoate and vilanterol	Reduces AE	Less reduction SGRQ Less reduction AE	Dysphonia
LABA, ICS and LAMA (41)	Fluticasone furoate, umeclidinium, and vilanterol	Improves FEV1	Compared to both LABA/LAMA and LABA/ICS	Pneumonia
		Reduces SGRQ	Improves FEV1	
		Reduces AE*	Reduces SGRQ Reduces AE	

*, greatest benefit in patients with eosinophils >300 cells/ μ L. SABA, short-acting bronchodilator agonist; SAMA, short-acting muscarinic agonist; FEV1, forced expiratory volume in 1 second; LABA, long-acting β_2 agonist; SGRQ, St. George Respiratory Questionnaire score; AE, acute exacerbation risk reduction; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

Table 3 Systemic therapies

Class of medication	Available medications	Benefits when compared to placebo	Adverse effects
PDE4 inhibitors (42)	Roflumilast	Increases FEV1	Diarrhea
		Reduces SGRQ	Weight loss
		Reduces AE	Exacerbation of psychiatric disorders
Macrolides (43)	Azithromycin	Reduces SGRQ	Hearing impairment
		Reduces AE	Arrhythmias

PDE4, phosphodiesterase 4; FEV1, forced expiratory volume in 1 second; St. George Respiratory Questionnaire score; AE, acute exacerbation risk reduction.

agonist or SABA and short-acting muscarinic antagonist or SAMA) and long acting (long-acting β_2 agonist or LABA and long-acting muscarinic antagonist or LAMA) therapies.

Short acting bronchodilators

Inhaled β_2 -agonists act through stimulation of β_2 -receptors in bronchial smooth muscle cells, increasing cyclic adenosine monophosphate (cAMP) and promoting airway relaxation and bronchodilation. Inhaled SABAs such as albuterol and levalbuterol have onset of action within 5–10 minutes and duration of 4–6 hours (34). Inhaled muscarinic antagonists block muscarinic receptors (M1, M2, and M3), thereby inhibiting the acetylcholine induced bronchial smooth muscle constriction. Ipratropium is a SAMA with effects lasting up to 8 hours (34). Both SABA and SAMA improve FEV1 and symptom relief in patients with all stages of COPD but should be not used as scheduled mono-therapy. Though there is no data to support SABA over SAMA monotherapy, combination therapy is superior to either medication alone in improving FEV1 and symptoms (33,34).

Long acting bronchodilators

Inhaled LABAs have bronchodilatory effects that last from 12 hours (formoterol or salmeterol) to 24 hours (indacaterol, olodaterol or vilanterol). Similarly, LAMAs have effects from 12 hours (aclidinium) to 24 hours (glycopyrronium, tiotropium, or umeclidinium). Both classes of medications are recommended as first-line therapy for patients with

higher symptom burden, exacerbations, or more severely impaired lung function (GOLD B-D). Both LABAs and LAMAs have been shown to improve FEV1, symptom scores, and reduce exacerbations (35,37). There are some data to support an advantage of tiotropium over LABAs as the most effective single agent in reducing exacerbations (36,37).

There are four FDA approved combination LABA/LAMA therapies (see *Table 2*). Combination LABA/LAMA therapies have shown greater efficacy in improving lung function, symptom burden and quality of life measures and in some studies, a reduction in moderate to severe exacerbation risk when compared with individual components (38,39). Of the four combination therapies, only indacaterol/glycopyrronium has demonstrated a reduction in exacerbation rate when compared to both LAMA and LABA/inhaled corticosteroids (ICS) (45). Current literature supports the safety of LABA/LAMA combination therapy with no increase in adverse events including cardiovascular events when compared with individual components (38,40).

ICS

Monotherapy with ICS is not recommended and has not shown any benefit with respect to improvement in lung function or mortality (46). In addition, treatment with ICS alone has been associated with increased risk of pneumonia, oropharyngeal candidiasis and hoarseness (46).

Combination inhaled therapies

Currently, combination dual and triple therapies are available in the market and approved by the FDA. Combination LABA/LAMA was discussed above. Combination of ICS and LABA improves lung function and quality of life and reduces acute exacerbations more than single components. Triple combination also improves lung function and quality of life and reduces rate of moderate or severe acute exacerbation more than single components (*Table 2*) (47).

Systemic corticosteroids

Systemic corticosteroids should be used in patients suffering from acute exacerbations of COPD and should not be used chronically for patients with stable COPD (48,49). A recent meta-analysis corroborates that a short course of oral

corticosteroids (3–7 days) is as effective as longer durations of treatment (10–15 days) with regards to treatment failure, relapse and time to next exacerbation with no difference in side effects (50).

PD4 inhibitors

Roflumilast is a selective inhibitor of phosphodiesterase-4 (PDE4) that increases intracellular cAMP leading to a variety of anti-inflammatory effects (51). Roflumilast is an oral medication initiated at 250 µg for the first four weeks and then continued at 500 µg daily (52). Roflumilast has demonstrated improvement in lung function in patients with moderate to severe COPD and decreased moderate exacerbations by 12.3% and severe exacerbations by 16.1% in patients with severe COPD associated with chronic bronchitis phenotype and a history of exacerbations (42,53). The most common adverse events with roflumilast include diarrhea, weight loss and insomnia and depressive mood symptoms, so caution should be taken when prescribing to patients who are underweight or have depression (42).

Macrolides

Macrolide antibiotics such as azithromycin have been shown to reduce exacerbations by 27% when taken daily (43). This is thought to be due to its immunomodulatory, anti-inflammatory and anti-bacterial properties at the expense of possible reversible hearing impairment and arrhythmias. This should be considered in patients who have exacerbations while on maximal inhaler therapy.

Stepwise approach to pharmacotherapy

Comprehensive COPD management is multifaceted. It includes pharmacologic management, patient education, smoking cessation, influenza and pneumococcal vaccination, depression and anxiety management, pulmonary rehabilitation, and if indicated, home oxygen therapy. The pharmacologic treatment choice primarily depends on two factors: (I) severity of symptoms and (II) frequency of exacerbations. There are multiple validated tools to objectively assess the severity of symptoms such as modified Medical Research Council (mMRC) and COPD Assessment Test (CAT). Frequency of exacerbations can be assessed based on number of exacerbations managed on outpatient basis and those that require hospitalization. In

patients with stable COPD, once the severity of symptoms and episodes of exacerbations are determined, medications can be started based on the COPD-GOLD framework (*Figure 1*). This classification provides a general framework which revolves around the following principles. In patients with limited symptoms and without exacerbations (group A), usually one bronchodilator is adequate. Short acting medications may be adequate to manage these patients, though in some cases, LAMA or LABA may be indicated. In patients with an exacerbation phenotype, LAMA has been shown to be superior, while in patients with an asthmatic phenotype, addition of ICS has shown to be helpful. If a single long-acting bronchodilator is not completely effective, combination therapy with LAMA and LABA is recommended. In COPD patients with high symptom burden (usually group D) and several exacerbations, “triple therapy” has been shown to be superior. Triple therapy involves a combination of LAMA, LABA and ICS (54–56). For patients who have chronic bronchitis with persistent symptoms despite triple therapy, addition of roflumilast should be considered. Macrolides for their anti-inflammatory benefits may be considered in those who are smokers.

With the complexity of pharmacologic therapy, non-pharmacologic therapy and risk reduction can be under appreciated (see smoking cessation and vaccination).

Once the initial therapy has been selected, close follow up to escalate and deescalate the pharmacologic therapy is indicated. *Figure 1* provides a general framework of treatment options for escalation and de-escalation. During the follow-up visits, in addition to clinical improvement, side effect profile should be considered. Several of these medications have significant side effects and associated risks which should be closely weighted with the benefits. For example, ICS are associated with a 1.57-fold increased risk for bacterial pneumonia (46). Patient education also plays a significant role in the overall management. Incorrect inhaler technique is a major factor contributing to treatment failure. Education about correct inhaler technique in addition to overall disease process either in individual and group settings has been shown to improve outcomes. Attention to patient’s and care giver’s inhaler device preferences is important (57). Prevalence of comorbid depression and anxiety is higher in patients with COPD compared to those without (58). This may lead to fatigue and ultimately activity avoidance. Screening of psychological conditions and comprehensive management with pulmonary rehabilitation improves symptoms, quality

of life, pulmonary function, and health care utilization.

Pulmonary rehabilitation

Respiratory rehabilitation is a multifaceted program encompassing several factors to improve the symptoms in COPD patients. A typical program is interdisciplinary and includes strength and endurance training as well as educational, psychological and nutritional training. These programs can improve cardiovascular fitness, symptoms and physical activity levels in patients with COPD (59).

Additionally, pulmonary rehabilitation has been shown to exceed improvements in dyspnea, exercise tolerance and quality of life to a degree that is greater than pharmacological therapies alone (60). Studies have shown that early respiratory rehabilitation following hospitalization for acute COPD exacerbation improves mortality [relative risk (RR) 0.58, 10% vs. 17.3%] and reduces the hospital readmission rate (RR 0.47) (61). Despite all these benefits, less than 5% of the eligible candidates receive the pulmonary rehabilitation (62). A typical respiratory rehabilitation program is attended about 2 to 3 times per week as part of overall COPD management. Medicare coverage however is limited to a maximum of 36 sessions with the option of an additional 36 sessions based on medical necessity.

Summary

COPD is a chronic medical condition with significant morbidity and mortality. A comprehensive assessment draws on subjective and objective data to classify patients in various severity and management groups. Vaccination and smoking cessation are indicated in all COPD patients. Bronchodilator therapy is the main recommended therapy. They improve symptoms, quality of life, lung function and exercise capacity, and reduce COPD exacerbation rate. Various anti-inflammatory agents may play a role in COPD management. They, in combination with long acting bronchodilators, improve various clinical outcomes. Further, patient education about the disease and about correct use of the prescribed medication is very important in a comprehensive management of this disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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