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Diagnosis and Outpatient Management of Chronic Obstructive Pulmonary Disease
A Review

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IMPORTANCE There are 30 million adults (12%) in the United States who have chronic obstructive pulmonary disease (COPD). Chronic obstructive pulmonary disease accounts for 3.2% of all physician office visits annually and is the fourth leading cause of death (126 000 deaths per year). Most patients are diagnosed by their primary care clinicians who must address the highly variable clinical features and responses to therapy. The diagnosis and treatment of COPD is rapidly changing, so understanding recent advances is important for the delivery of optimal patient care.

OBSERVATIONS Chronic obstructive pulmonary disease is characterized by incompletely reversible expiratory airflow limitation. Spirometry is the reference standard for diagnosing and assessing the severity of COPD. All patients should be counseled about and receive preventive measures such as smoking cessation and vaccination. Treatment should be guided by the severity of lung impairment, symptoms such as dyspnea, the amount of cough and sputum production, and how often a patient experiences an exacerbation. When dyspnea limits activity or quality of life, COPD should be treated with once- or twice-daily maintenance long-acting anticholinergic and β-agonist bronchodilators. Patients with acute exacerbations may benefit from the addition of inhaled corticosteroids, particularly those with elevated peripheral eosinophil levels. Pulmonary rehabilitation, which includes strength and endurance training and educational, nutritional, and psychosocial support, improves symptoms and exercise tolerance but is underutilized. Supplemental oxygen for patients with resting hypoxemia (defined as Spo_2 <89%) improves survival.

CONCLUSIONS AND RELEVANCE Chronic obstructive pulmonary disease is a complicated disease requiring intensive treatment. Appropriate use of long-acting maintenance bronchodilators, inhaled corticosteroids, and pulmonary rehabilitation decreases symptoms, optimizes functional performance, and reduces exacerbation frequency. Supplemental oxygen in patients with resting hypoxemia prolongs life, and other advanced treatments are available based on specific patient characteristics.

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Chronic obstructive pulmonary disease (COPD) is defined as incompletely reversible airflow obstruction associated with persistent respiratory symptoms including dyspnea, cough, and excessive sputum production. Although more than 75% of COPD diagnoses in the United States are related to tobacco smoke, other occupational or environmental particles, or gas exposures such as diesel exhaust and smoke from indoor cooking contribute to the development of COPD.[1] Chronic obstructive pulmonary disease is a heterogeneous syndrome caused by mechanistically distinct pathophysiological processes including innate and adaptive T_H1 type immune response to toxins, microbes, or autoimmunity; persistent T_H2 inflammation; antiprotease deficiency; and other mechanisms affecting the airways, alveoli, or both resulting in diverse clinical presentations, responses to treatment, and patterns of progression.

Chronic obstructive pulmonary disease is common, with 6.4% of the US population self-reporting a diagnosis.[2] Despite self-reported data, most patients with airflow obstruction on spirometry due to COPD have never been diagnosed, suggesting a more likely estimate of 29 million affected individuals.[3] Chronic obstructive pulmonary disease is the fourth leading cause of death in the United States.[4] Primary care physicians treat most patients with COPD.[5] This review provides practical information regarding the diagnosis and long-term management of patients with COPD in the outpatient setting.

Methods

We conducted a search of MEDLINE, Embase, and the Cochrane Database of Systematic Reviews for publications with the search words *COPD, chronic obstructive pulmonary disease,* or *chronic obstructive lung disease*. We searched for English-language publications between January 1, 2013, and November 1, 2018, with a focus on randomized clinical trials, meta-analyses, systematic reviews, and clinical practice guidelines. The MeSH (Medical Subject Headings) category for COPD was used to validate the results, and we performed a search of MEDLINE to identify 1091 additional unindexed publications. Additional publications preceding the search period were identified through bibliography review. A total of 2680 titles and abstracts were screened for relevance, and 456 articles were selected for full-text review by the authors. A total of 90 articles were referenced in this review: 26 clinical trials, 21 meta-analyses, 25 observational studies, and 18 guidelines and other reports.

Discussion

Presentation and Diagnostic Evaluation

Chronic obstructive pulmonary disease typically presents with 1 or more symptoms of exertional dyspnea, cough, sputum production, chest tightness, or fatigue. Symptoms may be underreported by patients who engage in minimal physical activity; therefore, clinicians should obtain a medical history that discerns whether patients have restricted their activity to avoid symptoms.[6] Formal dyspnea and symptom assessment tools such as the modified Medical Research Council (mMRC) dyspnea scale (0- to 4-point activity-anchored dyspnea scale, **Figure 1**) and the COPD assessment test (CAT) are recommended to stratify and monitor progression.[1,8-10] The CAT is an 8-question, 0- to 40-point symptom scale, including assessment of cough frequency, phlegm amount, chest tightness, tolerance to hill or stairclimbing, home activity level, confidence leaving home, sleep soundness, and energy level.

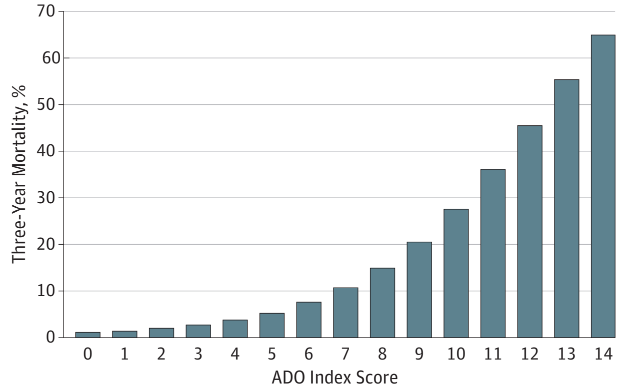
A history of exposure to inhaled particles or fumes such as tobacco smoke or indoor cooking supports the diagnosis of COPD. Although tobacco smoke is the primary risk factor in the United States and contributes to 75% of cases, smoke from wood and other fuels used for cooking and heating (odds ratio [OR], 2.3) and occupational dust and chemical fume exposures (OR, 1.7) are implicated in about 25% of patients with COPD who never smoked.[11] Premature birth, severe childhood respiratory infections, and poorly controlled asthma are associated with lower peak adult lung function, which increases the odds of COPD following exposures by as much as 12.5-fold.[11-13]

Spirometry is the reference standard for diagnosing and assessing severity of COPD. If obstruction is present on spirometry, a short-acting bronchodilator should be administered and the patient retested in 15 minutes to establish the diagnosis of incompletely reversible obstruction, the hallmark of COPD. The Global Initiative for Chronic Obstructive Lung Disease[1] (GOLD) guidelines recommend using a fixed ratio of 0.7 of the forced expiratory volume in the first second of the forced vital capacity (FEV_1/FVC) to establish a diagnosis of obstruction. This criterion, however, tends to overdiagnose disease in older adults and underdiagnose disease in younger adults when compared with a population-derived, age-adjusted lower limit of normal. Use of the lower limit of normal to define disease is controversial because patients with FEV_1/FVC higher than the lower limit of normal but lower than 0.7 have a higher risk of death and COPD-related hospitalization than do those who have normal values by both cutoffs.[14] Population-based spirometric screening is not recommended; rather, spirometry should be obtained from patients who describe chronic respiratory symptoms and a history of exposures.[15]

Physical examination is useful for assessing signs of lung hyperinflation in advanced disease or to rule out alternative diagnoses related to nonpulmonary organ involvement. Adventitious breath sounds such as wheezing and rhonchi are seldom present in stable COPD may indicate an acute exacerbation, whereas rales suggest

Figure 1. Dyspnea and Symptom Assessment Tools

Association of the Age, Dyspnea, and Airflow Obstruction (ADO) Index Score With Mortality



Calculation of the ADO Index Score

The ADO index score is calculated by assigning points to 3 clinical components (age, mMRC dyspnea score, FEV_1), as shown in the table below, and summing the total points.

ADO Index Clinical Components	ADO Index Point Assignment 0	1	2	3	4	5	7
Age, y	40-49		50-59		60-69	70-79	≥80
mMRC Dyspnea Score	0	1-2	3	4			
FEV_1 (% predicted)	≥81	65-80	51-64	36-50	≤35		

Determination of the mMRC Dyspnea Score

Scoring for the mMRC Dyspnea Scale is shown in the table below.

mMRC Dyspnea Scale	Score
Not troubled by breathlessness except with strenuous exercise	0
Breathless when hurrying on level ground or walking up a slight hill	1
Walks slower than people of the same age because of breathlessness or has to stop for breath when walking at own pace on level ground	2
Stops for breath after walking 100 yards (90 m) or after a few minutes on level ground	3
Too breathless to leave the house or breathless when dressing or undressing	4

In contrast to other mortality risk scores validated for COPD, the ADO index relies only on clinical measures easily obtained in general clinical practice (age, FEV_1% predicted, mMRC dyspnea score). This model predicts 3-year mortality, providing the clinician with useful prognostic information to risk stratify patients.

Abbreviations: FEV_1: forced expiratory volume in the first second of expiration; mMRC, modified Medical Research Council; % predicted, percent predicted of normal;

The Age, Dyspnea, and Airflow Obstruction (ADO) Index was developed and validated by and adapted from Puhan et al.[7] The modified Medical Research Council Dyspnea Scale was adapted from Mahler and Wells.[8]

pulmonary fibrosis or congestive heart failure. Auscultation of prolonged air flow at the trachea during a maximal forced effort can be useful in early diagnosis of obstruction or when spirometry is unavailable. A case series[16] involving 95 patients reported a maximal forced expiratory flow time that exceeds 6 seconds had a sensitivity of 81% and specificity of 100% for identifying an FEV_1/FVC of less than 0.65.

Resting pulse oximetry is recommended for patients presenting with dyspnea to evaluate the need for supplemental oxygen therapy. Computed tomographic (CT) imaging, while not required for diagnosing COPD, is recommended by some experts when patients do not respond as expected to treatment to rule out comorbid pulmonary conditions such as bronchiectasis or pulmonary fibrosis. Screening for α_1-antitrypsin deficiency is recommended for all patients with COPD because only 5% of patients with the deficiency have been diagnosed, and intravenous infusion of the α_1-antitrypsin protein in individuals with moderate to severe obstruction due to α_1-antitrypsin deficiency can slow emphysema progression.[17-19]

Low-dose CT screening for lung cancer has demonstrated early detection and reduced relative all-cause mortality by 6.7% and relative lung cancer–specific mortality by 20% (absolute rates of 2.47 vs 3.09 lung cancer deaths per 1000 patient-years with CT and radiographic screening, respectively) in appropriately selected patients (between age 55 and 80 years, 30 or more pack-year smoking history, currently smoking or quit within 15 years, and life expectancy not limited by another end-stage disease).[20] Lung cancer risk is higher among patients with COPD, and the presence of radiographic emphysema is associated with a 3.3-fold relative risk (RR) of malignancy in an incidentally discovered pulmonary nodule compared with age- and smoking-matched controls.[21,22]

Prognosis and Risk Stratification

The assessment of risk of future acute exacerbations and death is important for setting patient expectations and treatment planning. Patients with history of a single COPD exacerbation requiring hospitalization (categorized as a severe exacerbation) have a higher risk of future severe exacerbations (RR, 1.71).[23,24] Risk of mortality can be predicted using the age, dyspnea, airflow obstruction (ADO) index, which incorporates age, mMRC dyspnea scale, and FEV_1, measures that are easily accessible in a primary care setting (Figure 1). The body mass, obstruction, dyspnea, exercise (BODE) index also predicts mortality and incorporates the negative prognostic implications of a body mass index of 21 or less, FEV_1, mMRC, and the 6-minute walk test (area under the receiver operating characteristic, 0.694 for the ADO index vs 0.679 for the BODE index).[7,25] (Body mass index is calculated as weight in kilograms divided by height in meters squared.)

Approach to Treatment

Medical treatment of COPD reduces symptom burden and decreases exacerbation risk. Initial therapy should be guided by the patient's symptom burden, exacerbation risk, and severity of lung function impairment. Therapies can be intensified, added, or withdrawn based on the patient's response and subsequent clinical course.

Smoking cessation using a combination of behavioral and pharmacological treatment (including nicotine replacement therapy, bupropion, and varenicline) is effective and should be encouraged at every visit.[26] Annual influenza vaccination reduces COPD exacerbations.[27] Pneumococcal vaccinations should be administered according to Centers for Disease Prevention and Control guidelines, which support the use of 23-valent pneumococcal polysaccharide vaccine (PPSV-23 [Pneumovax]) for all patients with COPD or who are current smokers.[28] The 13-valent pneumococcal conjugate vaccine (PCV-13 [Prevnar]) is recommended for patients with COPD who are 65 years or older and for younger patients with frailty or who require frequent systemic steroids.

Bronchodilators

Bronchodilators are separated into 2 major classes by their mechanisms of action and are the mainstay of COPD treatment. β_2-Agonists bind to β_2-adrenergic receptors on airway-smooth muscle cells, promoting bronchodilation and increasing ciliary beat frequency. Muscarinic antagonists block M_1 and M_3 muscarinic receptors, preventing parasympathetic bronchoconstriction of airway-smooth muscle and inhibiting goblet cell mucus secretion. Although oral bronchodilators are available, delivery through inhalation improves efficacy and decreases adverse effects.

Short-acting bronchodilators include short-acting β_2-agonists (SABAs) albuterol and levalbuterol and the short-acting muscarinic antagonist (SAMA) ipratropium. They may be used as needed alone or in combination for patients with limited symptoms or activity-specific dyspnea but are not appropriate as scheduled therapies for patients with a history of exacerbations or persistent symptoms. Escalation to long-acting maintenance bronchodilator treatment is recommended for patients using short-acting bronchodilators more than 2 to 3 times per week. Bronchodilators can improve symptoms by reducing lung hyperinflation and improving inspiratory muscle efficiency even in patients without spirometric evidence of bronchodilator reversibility.

For patients with higher symptom burden (mMRC ≥2, CAT ≥10), prior exacerbations or more severely impaired lung function (FEV_1 <60% predicted), long-acting bronchodilators in daily or twice daily preparations are indicated.[30,31] Both long-acting β_2-agonists (LABAs) such as formoterol, vilanterol, olodaterol, indacaterol, or arformoterol and long-acting muscarinic antagonists (LAMAs) such as tiotropium, umeclidinium, glycopyrrolate, aclidinium, or revefenacin reduce symptom scores and decrease exacerbation risk (**Table 1**, **Figure 2**), with LAMAs being the most effective single agent (RR of exacerbation with LAMA, 0.86 vs LABA).[41] Combination dual long-acting bronchodilator therapy containing both LAMAs and LABAs—tiotropium plus olodaterol, vilanterol plus umeclidinium, indacaterol plus glycopyrrolate, or formoterol plus glycopyrrolate—provide greater average improvement in lung function (by 80 mL), symptom scores (St George Respiratory Questionnaire score decreased by 2.3 U), and exacerbation risk (13% lower) when compared with the individual components.[35] Thus, the authors favor initiating treatment with combination LAMA and LABA agents rather than with single agents for patients with either high initial symptom burden or a history of exacerbations.

The risk of major cardiac adverse events with long-acting bronchodilators is not different from placebo in clinical trials and is similar in dual- compared with single-component regimens.[42] Risks may be underrepresented in clinical trials that often exclude patients with coronary artery disease, heart failure, or tachyarrhythmias.[43-45]

Table 1. Pharmacotherapy for COPD

Source	Class	Mechanism of Action	Medication Dose	Frequency	Device	Benefits[a]	Adverse Effects, %[b]
Short-Acting Inhaled Rescue Medications							
Combivent Inhalation Aerosol Study Group,[29] 1994	β_2-Agonist	Bronchodilation via airway smooth muscle β_2 receptor stimulation	Albuterol 180 or 200 µg	Every 4-6 h	pMDI, DPI	Mean peak effect vs placebo ↑FEV_1 170 mL	Headache, 3-5 Tachycardia, 2-3 Nasopharyngitis, 0-5 Muscle pain, 0-3 Dizziness, 0-3
			Albuterol 2.5 mg	Every 4-6 h	Nebulizer		
			Levalbuterol 90 µg	Every 4-6 h	pMDI		
			Levalbuterol 0.63 mg	Every 4-6 h	Nebulizer		
	Muscarinic antagonist	Inhibition of bronchoconstriction via airway smooth muscle M_1 and M_3 receptor blockade	Ipratropium 34 µg	4/d	pMDI	Mean peak effect vs placebo ↑FEV_1 170 mL	Dry mouth, 2 Nausea, 2 Flu-like symptoms, 2
			Ipratropium 0.5 mg	4/d	Nebulizer		
	Muscarinic antagonist and β_2-agonist combination	Bronchodilation via combination β_2 agonism and M_1 and M_3 receptor antagonism	Albuterol 100 µg and ipratropium 20 µg	4/d	SMI	Mean peak effect vs placebo, ↑FEV_1 240 mL	No difference vs monocomponents
			Albuterol 2.5 mg and ipratropium 0.5 mg	Every 4-6 h	Nebulizer		
Long-Acting Inhaled Maintenance Medications							
Karner et al,[32] 2014; Kew et al,[33] 2014	Muscarinic antagonist	Inhibition of bronchoconstriction via airway smooth muscle M_1 and M_3 receptor blockade	Aclidinium 400 µg	2/d	DPI	Mean peak effect vs placeb ↑FEV_1, 104 mL (82-125) ↓SGRQ, 2.6 U (2.0-3.5) ↓AE risk, 0.78 (0.70-0.87)[d]	Nasopharyngitis, 1-2 Dry mouth, 0-2
			Glycopyrrolate 15.6 µg	2/d[c]	DPI		
			Glycopyrrolate 25 µg	2/d	Nebulizer		
			Tiotropium 18 µg	Daily	DPI		
			Tiotropium 5 µg	Daily	SMI		
			Umeclidinium 62.5 µg	Daily	DPI		
			Revefenacin 88 µg	Daily	Nebulizer		
Kew et al,[33] 2014; Kew et al,[34] 2013	β_2-Agonist	Bronchodilation via airway smooth muscle β_2 receptor stimulation	Arformoterol 15 µg	2/d	Nebulizer	Mean peak effect vs placebo ↑FEV_1, 99 mL (72-128) ↓SGRQ, 2.3 U (1.5-3.2) ↓AE risk, 0.88 (0.76-1.02)	Nasopharyngitis, 1-3 Headache, 0-3 Muscle cramp, 1-2 Arthralgia, 0-2
			Formoterol 12 µg	2/d	DPI		
			Formoterol 20 µg	2/d	Nebulizer		
			Indacaterol 75 µg	Daily	DPI		
			Olodaterol 5 µg	Daily	SMI		
			Salmeterol 50 µg	2/d	DPI		
Oba et al,[35] 2016	Muscarinic Antagonist and β_2-agonist combination	Bronchodilation via combination β_2 agonism and M_1 and M_3 receptor antagonism	Glycopyrrolate 18 µg and formoterol 9.6 µg	2/d	pMDI	Mean peak effect vs placeb ↑FEV_1, 210 mL (190-230) ↓SGRQ, 4.6 U (3.3-5.9) ↓AE risk, 0.66 (0.57-0.77) vs LABA ↑FEV_1, 100 mL (80-130) ↓SGRQ, 2.3 U (1.3-3.3) ↓AE risk, 0.82 (0.73, 0.93) vs LAMA ↑FEV_1, 60 mL (50-80) ↓SGRQ, 2.3 U (1.7-2.9) ↓AE risk, 0.92 (0.84-1.00)	Nasopharyngitis, 1-2
			Indacaterol 27.5 µg and glycopyrrolate 15.6 µg	2/d[c]	DPI		
			Olodaterol 5 µg and tiotropium 5 µg	Daily	SMI		
			Umeclidinium 62.5 µg and vilanterol 25 µg	Daily	DPI		

(continued)

Table 1. Pharmacotherapy for COPD (continued)

Source	Class	Mechanism of Action	Medication Dose	Frequency	Device	Benefits[a]	Adverse Effects, %[b]
Kew et al,[33] 2014; Rodrigo et al,[36] 2017; Nannini et al,[37] 2013	β_2-Agonist and ICS combination	Bronchodilation via airway smooth muscle β_2 receptor stimulation and decreased airway inflammation	Budesonide 320 µg and formoterol 9 µg	2/d	pMDI[e]	Mean peak effect vs placebo ↑FEV_1, 133 mL (101-164) ↓SGRQ, 3.9 U (3.0-4.7) ↓AE risk, 0.73 (0.69-0.78) vs combination LAMA and LABA ↓FEV_1, 60 mL (0-120) ↑SGRQ, 1.13 U (0.5-1.8) ↓AE risk, 1.22 (1.10-1.33)	Pneumonia, 3 Candidiasis, 1-9 Dysphonia, 1-5 Headache, 1-4 Nasopharyngitis, 1-2
			Fluticasone propionate 250 µg and salmeterol 50 µg	2/d	DPI		
			Fluticasone furoate 100 µg and vilanterol 25 µg	Daily	DPI		
Zeng et al,[38] 2018	Muscarinic antagonist, β_2-agonist, and ICS combination	Combination bronchodilation via β_2 agonism and M_1 and M_3 receptor antagonism and decreased airway inflammation	Fluticasone furoate 100 µg, umeclidinium 62.5 µg and vilanterol 25 µg	Daily	DPI	Mean peak effect vs combination LAMA and LABA ↑FEV_1, 40 mL (20-70) ↓SGRQ, 1.81 U (1.04-2.57) ↓AE risk, 0.78 (0.70-0.88) Vs combination LABA and ICS ↑FEV_1, 110 mL (100-130) ↓SGRQ, 1.81 U (1.35-2.28) ↓AE risk, 0.77 (0.66-0.91)	Increase in event rate vs non-ICS regimens pneumonia: 3 vs combination LABA and ICS back pain, 2 Diarrhea, 1-2
Oral Medications							
Chong et al,[39] 2017	PDE4 inhibitors	Decreased airway inflammation and increased bronchodilation via inhibition of cAMP breakdown in inflammatory and airway smooth muscle cells	Roflumilast 500 µg	Daily	Tablet	Mean peak effect vs placebo ↑FEV_1, 52 mL (43-60) ↓SGRQ, 1.1 U (0.4-1.7) ↓AE risk, 0.78 (0.73-0.83)	Diarrhea, 7 Weight loss, 6 Any psychiatric disorder, 4 Nausea, 3 Headache, 2
Albert et al,[40] 2011	Macrolides	Decreased airway inflammation from decreased bacterial burden +/− impaired neutrophil chemotaxis	Azithromycin 250 mg[f]	Daily	Tablet	Mean peak effect vs placebo ↓SGRQ, 2.2 U (0.7-3.7) ↓AE risk, 0.83 (0.72-0.96)	Hearing impairment, 6

Abbreviations: AE risk, acute exacerbation risk reduction; cAMP, cyclic adenosine monophosphate; down arrow, decreasing; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, log-acting muscarinic antagonist; PDE4, phosphodiesterase 4; pMDI, pressurized metered dose inhaler; SGRQ, St George Respiratory Questionnaire total score; SMI, soft mist inhaler; up arrow, increasing.

[a] Benefit effect sizes are presented as mean or mean (interquartile range) and are given for all pooled medications within each class except as noted; minimum clinically important differences for FEV_1 and SGRQ are 100 mL and 4 U, respectively.

[b] Adverse effects listed have an increased incidence of 2% or more compared with placebo for any individual medication and are compiled from US Food and Drug Administration product labels and cited analyses.

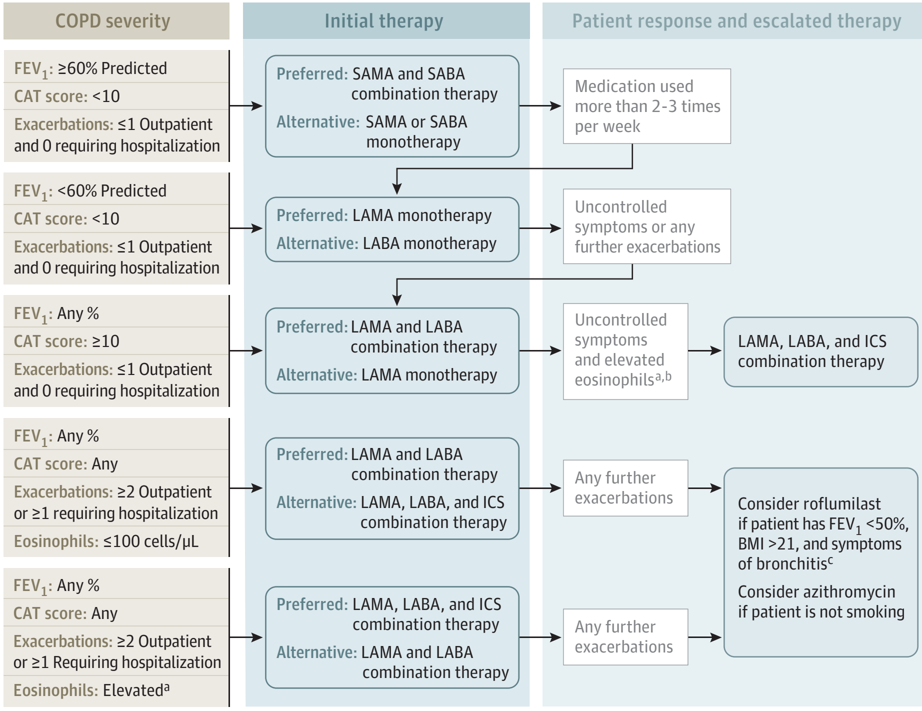
[c] Dosing frequency differs outside of United States.

[d] Exacerbation risk reduction data presented for tiotropium only.

[e] Device availability differs outside of United States.

[f] Off-label use allows for 250 to 500 mg 3 times weekly dosing.

Figure 2. Medical Treatment Algorithm for Chronic Obstructive Pulmonary Disease



Initial medical treatment of chronic obstructive pulmonary disease (COPD) is guided by severity of obstruction, symptom burden, and exacerbation risk with escalation in therapy targeted to control persistent symptoms or further exacerbations. Exacerbation severity is differentiated by the location of treatment, with moderate exacerbations treated in the outpatient setting with oral corticosteroids, antibiotics, or both and severe exacerbations requiring hospitalization or emergency department care. Additional therapies such as azithromycin and roflumilast can be considered for select patients who continue to experience exacerbations despite optimal inhaled therapy. Further therapies such as azithromycin and roflumilast can be considered in select patients with persistent exacerbations despite maximal inhaled therapy. BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared; CAT, COPD assessment test; FEV_1, forced expiratory volume in the first second of expiration; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist.

[a] Higher blood eosinophil levels predict increasing therapeutic response to ICS along a continuous spectrum; however, levels of 100 cells/μL or less have been associated with minimal benefit.

[b] Patients taking combined LABA and LAMA therapy who do not have elevated eosinophils do not have an additional available recommended pharmacological therapeutic option.

[c] Patients taking roflumilast who continue to exacerbate do not have an additional available recommended therapeutic option.

Inhaled Corticosteroids

Inhaled corticosteroids decrease airway inflammation and are the first-line treatment of asthma. In COPD, modest improvements in lung function and significant decreases in exacerbation rates are observed when inhaled corticosteroids are added to combined LAMA and LABA therapy as observed in 3 large trials with an observed exacerbation RR of 0.75 in the IMPACT[46] trial, 0.85 in the TRIBUTE[47] trial, and 0.48 in the KRONOS[48] trial (absolute moderate to severe exacerbation rate reductions of 1.21 to 0.91, 0.59 to 0.50, and 0.95 to 0.46 per year in each trial, respectively) with combination inhaled corticosteroids and combined LAMA and LABA therapy compared with combined LAMA and LABA therapy alone (Table 1).[46-48] The benefits of inhaled corticosteroids must be balanced against the 1.57-fold increased risk of bacterial pneumonia. Other complications increased vs placebo include thrush (9%), hoarseness (5%), and skin bruising (8%). Thrush can be mitigated by encouraging patients to rinse their mouths after inhaled corticosteroids use and by using a spacer with pressurized metered dose inhalers.[49,50]

Peripheral blood eosinophil levels obtained from a routine complete blood count are a useful biomarker to select patients with the most favorable risk to benefit ratio for inhaled corticosteroid treatment. In each of the above trials comparing inhaled corticosteroid–based triple therapy to dual bronchodilator therapy, subgroup analysis stratified by peripheral blood eosinophil levels of 150 cells/μL or 2% of the white blood cell differential suggested a significantly greater response to inhaled corticosteroids in the high-eosinophil group. Specifically, in the IMPACT trial, inhaled corticosteroid–based triple therapy resulted in 30 fewer exacerbations per 100 patient-years than did patients treated with combination LAMA and LABA therapy. For patients with peripheral blood eosinophil levels of 150 cells/μL or higher, the use of inhaled corticosteroid treatment reduced the exacerbation event rate by 44 per 100 patient-years, whereas patients levels lower than 150 cells/μL had a reduction of only 12 events per 100 patient-years. These effects must be balanced against an increase in pneumonia rates of 3.6 per 100 patient-years in the inhaled corticosteroid group. A retrospective analysis[51] comparing combined inhaled corticosteroid and LABA with LABA alone further substantiated these findings. Patients with peripheral blood eosinophil levels of less than 100 cells/μL demonstrated no benefit with the addition of inhaled corticosteroids for

Table 2. Inhaled Medication Use

	Powered Metered Dose Inhaler	Soft Mist Inhaler	Dry Powder Inhaler Single Dose	Dry Powder Inhaler Multidose	Nebulizer
Description	Medication and propellant contained in a pressurized canister and propelled through a nozzle for inhalation	Medication is propelled by a spring-loaded mechanism through a nozzle for inhalation	Encapsulated medication is loaded prior to each dose, which is pierced by the device and delivered by patient inspiratory effort	Doses of preloaded medication are delivered by patient inspiratory effort	Medication is aerosolized by an air jet, ultrasonic energy, or vibrating mesh and can be inhaled during normal tidal breathing
Directions	1. Shake for 5 s 2. Attach spacer (if available) 3. Fully exhale and then place lips on the inhaler (or spacer) 4. While pressing down on the top of the inhaler, inhale slowly and deeply for at least 3 s 5. Hold breath for 10 s or as long as is comfortable 6. Wait 1 min, then repeat if a second dose is prescribed	1. With the cap closed, twist the clear base ½ turn. Do not shake 2. Open the cap and hold the inhaler horizontally 3. Fully exhale and then place lips on the inhaler, making sure to not cover the side vents 4. While pressing the button, inhale slowly and deeply for at least 3 s 5. Hold breath for 10 s or as long as is comfortable 6. A second dose can be given without waiting	1. Remove and open cap 2. Open the inhaler and place one capsule from a sealed blister pack into the chamber 3. Close the inhaler 4. Pierce the capsule once and fully release the button 5. Exhale fully away from the device and then place lips on the device, holding it horizontally 6. Inhale with a forceful, deep breath for 2-3 s 7. Hold breath for 10 s or as long as is comfortable 8. Exhale away from the device 9. Open the device and discard the capsule	1. Slide the cover until it clicks 2. Exhale fully away from the device 3. Place lips on the device holding it horizontally 4. Inhale with a forceful, deep breath for 2-3 s 5. Hold breath for 10 s or as long as is comfortable 6. Exhale away from the device and close the cover	1. Load 1 dose of medication into the nebulizer chamber according to medication and nebulizer instructions 2. Sit relaxed in an upright position 3. Place the mouthpiece in the mouth and turn on the nebulizer 4. Breathe normally until the medication has been fully nebulized to receive the correct dose, usually 3-10 min depending on nebulizer type 5. Turn off the nebulizer 6. Clean and disinfect the reservoir and mouthpiece according to device instructions
Advantages	Patient familiarity Low inspiratory flow	Low inspiratory flow	Ease of use	Ease of use	No coordination or special breathing techniques Low inspiratory flow
Pitfalls	Requires coordination of inhalation and actuation (improved with spacer)	Device assembly Requires some coordination of inhalation	Inadequate inspiratory flow rate Improper handling of capsules	Inadequate inspiratory flow rate Exposure to moisture by exhaling into the device or storing it in high-moisture settings	Less portable Requires frequent cleaning

outcomes of symptom score, FEV_1 and exacerbation rate, whereas the relative response in all measures improved with increasing eosinophil levels above 100 cells/μL. The greatest relative improvement was observed with peripheral blood eosinophil levels of more than 300 cells/μL. The authors used peripheral blood eosinophil as a continuous biomarker in conjunction with other clinical features including exacerbations and a history of asthma or other allergic conditions when considering initiation of inhaled corticosteroid–based treatment.

Withdrawal of inhaled corticosteroids should be considered for patients who demonstrate prolonged stability of at least 2 years without a moderate to severe exacerbation or for whom inhaled corticosteroids have been inappropriately started based on current guidelines. In the WISDOM trial,[52] patients with severe obstruction (FEV_1 <50% predicted) and at least 1 exacerbation in the prior year were randomized after a run-in period on triple therapy to either continued triple therapy or to combination LAMA and LABA therapy with discontinuation of inhaled corticosteroids. Exacerbation frequency was equivalent in both treatment groups suggesting that inhaled corticosteroids can be safely withdrawn for many patients. A post hoc subgroup analysis found that following withdrawal, patients with peripheral blood eosinophil of 2% or higher had a 22% greater risk of exacerbation than did patients with lower levels.[53] These results have been prospectively replicated in the SUNSET trial,[54] which also showed that peripheral blood eosinophil levels should be considered when withdrawing inhaled corticosteroid–based therapy.

Variety of Compounds and Devices Within Drug Classes

The number of specific pharmacological compounds and unique delivery devices have increased over the last 2 decades. Although direct comparison of different LAMA, LABA, and inhaled corticosteroid compounds and combinations have demonstrated differences in FEV_1 improvement, longer head-to-head studies establishing superiority of individual drugs at improving symptoms or exacerbation risk are not available.[55,56] Considerations such as formulary, cost, inhaler device attributes, and patient preference should influence decisions about which inhaler to prescribe. Switching between drugs and devices in the same therapeutic category when patients do not respond as expected can be effective.

Adherence to inhaled medications, defined as the technically correct use of the device at the scheduled time for at least 80% of prescribed doses, is as low as 6%.[57] Proper adherence is associated with improved treatment efficacy, decreased hospitalization for exacerbations, and improved survival.[58] Three classes of inhaler devices are routinely used: pressurized metered dose inhalers, dry powder inhalers, and soft mist inhalers. Clinicians should be prepared to offer in-person inhaler technique assessment and training (**Table 2**). Web-based demonstrations are available to assist with training, including a mobile app offered through the nonprofit COPD Foundation.[31]

Pressurized metered dose inhalers require timing of inhalation with actuation and greater dexterity to coordinate activation, whereas dry powder devices are breath activated only during inspiration. Soft mist inhalers are less sensitive to actuation coordination errors than pressurized metered dose inhalers but require greater dexterity to assemble. A meta-analysis[59] identified error rates of 86.8% in pressurized metered dose inhaler usage compared with 60.9% for dry powder inhaler use. Furthermore, face-to-face teaching time required to restore mastery of the device was 8 minutes longer for pressurized metered dose inhalers vs 5 minutes with dry powder inhalers.[60] Dry powder inhalers require a greater inspiratory flow to deliver medication to the lower airways (>40-60 L/min) than pressurized metered and soft mist inhalers (>20 L/min), which can result in inadequate delivery particularly in older patients, women, and those with short stature or decreased forced vital capacity.[61] Portable devices to assess inspiratory flow adequacy against simulated device resistance are available.[62] Long-acting nebulizer therapy, now available for all inhaled drug classes, is an alternative when patients are unable to use inhalers despite instruction. Long-acting nebulizer therapy, now available for all inhaled drug classes, is an alternative when patients are unable to use inhalers despite instruction. In patients able to properly use inhalers, however, nebulized therapy does not confer better drug delivery or additional clinical benefit.

Long-term Oxygen Therapy

Oxygen therapy improves survival in patients with advanced lung disease who have hypoxemia at rest (Spo_2 <89% or Pao_2 ≤55 mm Hg).[63,64] Patients with evidence of right-heart dysfunction on physical examination or with polycythemia may also benefit from supplemental oxygen with a Pao_2 of 59 mm Hg or lower. Treating patients who develop hypoxemia only during exercise can improve exertional dyspnea in some patients but is not associated with improved survival or other health benefits.[65,66] It is unknown whether treating isolated nocturnal hypoxemia in nonhypercapnic patients without sleep apnea provides benefit. Pending definitive evidence, the authors offer nocturnal oxygen to patients with isolated nocturnal desaturations ($Spo_2 \leq 88\%$ for >5 minutes of the night).

Pulmonary Rehabilitation

Pulmonary rehabilitation programs incorporate strength and endurance training and educational and nutritional and psychosocial support and can improve cardiovascular fitness, physical activity levels, and symptoms in patients with COPD.[67] Pulmonary rehabilitation improves dyspnea, exercise tolerance, and quality of life to a greater degree than pharmacological therapies.[68] Despite these benefits, fewer than 5% of eligible patients receive pulmonary rehabilitation.[69] Patients with functional impairment and those unable or unwilling to perform independent exercise training can benefit from supervised pulmonary rehabilitation. Furthermore, early pulmonary rehabilitation following hospitalization for an acute exacerbation of COPD improves mortality (RR, 0.58, 10.0% vs 17.3%) and reduces hospital readmissions (RR, 0.47).[70] Pulmonary rehabilitation program sessions are commonly attended 2 to 3 times per week; Medicare coverage is limited to a maximum of 36 sessions with the option for an additional 36 sessions over a lifetime if medically necessary.

Outpatient Management of Acute Exacerbations

Acute exacerbations of COPD are defined as episodes of increasing respiratory symptoms, particularly dyspnea, cough and increased sputum production, and purulence. Exacerbations negatively affect quality of life, promote decline in lung function, and may result in hospitalization and death.[71]

Mild exacerbations generally resolve with increased frequency of rescue short-acting bronchodilators. Moderate exacerbations, defined in clinical trials and prediction models as those requiring systemic steroids or antibiotics, can be managed in the outpatient setting. Short durations of oral corticosteroids (30-40 mg of prednisone equivalent for 3-7 days) are equally as effective as prolonged regimens (10-15 days) with respect to treatment failure, relapse, time to next exacerbation, and recovery of lung function following treatment with fewer adverse effects.[72] Antibiotic treatment reduces the risk of treatment failure and increases the time to next exacerbation, although the effect is modest and likely attributable to a subgroup of patients with a bacterial etiology.[73] Given the common occurrence of bacterial colonization in patients with COPD, sputum culture is not useful in defining a bacterial etiology; thus, oral antibiotics such as trimethoprim plus sulfamethoxazole, doxycycline, or macrolides are recommended as first-line treatment in patients exhibiting increasing sputum volume and purulence, while quinolones or ampicillin plus clavulanate are considered for patients with repeated exacerbations or suspected bacterial resistance.[73]

Dyspnea or tachypnea at rest unrelieved with short-acting bronchodilators, fever, chest pain, or increasing lower-extremity edema are characteristic of severe exacerbations and warrant face-to-face urgent or emergency evaluation. Fever or localized chest discomfort may represent pneumonia and requires chest radiography. Hospitalization is appropriate for patients with new or worsening hypoxemia, persistent dyspnea, acidemia, or tachypnea at rest following clinician-administered bronchodilators and systemic steroids, altered mentation, or accessory muscle use and overt respiratory distress. A lower threshold for hospital admission should be considered for elderly or frail patients, those with severe baseline disease and patients with cardiac or cognitive comorbidities, especially in situations with inadequate home caregiver support. Following emergency department evaluation or hospitalization, patients should be contacted within 48 hours to verify stability and should follow-up in the outpatient setting within 1 week to confirm resolution and to optimize therapy to prevent recurrence.

Approach to the Patient With Persistent Symptoms or Recurrent Exacerbations

Expiratory airflow obstruction is treatable in all patients with COPD. However, other clinical characteristics differ between individuals and can affect patient-centered outcomes. Variation in the contribution of parenchymal emphysema vs chronic bronchitis or the degree of lung hyperinflation and diffusion impairment occur for any given level of airflow obstruction. Other associated pulmonary pathology and systemic comorbidities can also independently influence symptoms and outcomes.[5,74]

Assessment of Comorbidities

Patients with COPD are at increased risk of other systemic conditions disproportionate to shared risk factors (eg, tobacco exposure). The presence of these comorbidities may mimic COPD symptoms or exacerbations.

Chronic obstructive pulmonary disease is independently associated with a higher prevalence of coronary artery disease and hypertension. Coexistence of heart failure may contribute to worsening symptoms.[75] Gastroesophageal reflux related to lung hyperinflation associated with loss of integrity of the gastroesophageal sphincter predisposes to impaired deglutition, reflux, microaspiration, and increased risk of lower respiratory tract infections and to COPD progression. Obstructive sleep apnea occurs in approximately 30% of patients with COPD and contributes to fatigue and decreased functional status.[76] Patients with COPD have an 85% greater prevalence of anxiety than the general population (15.1% vs 6.3% overall prevalence, respectively), and depression is associated with poor adherence to medications and increased hospitalization rates.[77,78] Limb muscle dysfunction and cachexia are prevalent in COPD and are associated with increased hospitalization rates and death.[79] Osteopenia occurs at a 2.2- to 3.6-fold higher rate in patients with mild or more severe emphysema (53.6% prevalence in patients without emphysema vs 71.8% with trace to mild and 80.6% with moderate to severe emphysema).[80] In the setting of COPD, osteoporosis related vertebral compression fractures can further decrease lung function.

Other Associated Pulmonary Disease

Other pulmonary diseases are also common in patients with COPD. Pulmonary fibrosis can present with dyspnea on exertion disproportionate to the degree of spirometric obstruction and is often reflected in relatively preserved expiratory flow but worsening diffusion impairment and hypoxemia. Atypical mycobacterial infection can lead to slowly progressive pulmonary infiltrates and increasing symptoms. The overlapping presence of bronchiectasis and COPD is poorly understood and is associated with greater symptoms, more frequent exacerbations, and poorer prognosis. Asthma overlap, represented by more than 12% bronchodilator reversibility and a significant history of allergy or prior asthma, should prompt the earlier use of inhaled corticosteroids.

Additional Testing

Repeating spirometry yearly can identify lung function decline and is recommended by some experts, although the impact on patient outcomes has not been studied. More complete testing including diffusing capacity and plethysmographic lung volume measurements can identify impairments in gas diffusion or hyperinflation that may disproportionately influence symptoms. Assessment of exertional oxygen saturation with pulse oximetry with a laboratory-based treadmill test or a clinician-accompanied hall walk or stair climb can identify exertional hypoxemia as a cause of exercise intolerance. Echocardiography should be considered when dyspnea is disproportionate to lung dysfunction or not responsive to treatment.

Pharmacological Therapy for Patients With Persistent Exacerbations

Roflumilast, an oral phosphodiesterase-4 inhibitor, has anti-inflammatory properties in patients with COPD. In the subset of patients with severe obstruction, frequent exacerbations and symptoms of chronic bronchitis, roflumilast decreased moderate or severe exacerbations by 14.3% over 1 year (0.52 exacerbations vs 0.61 exacerbations with roflumilast or placebo, respectively).[81] Gastrointestinal adverse events (nausea, diarrhea, weight loss) may lead to significant rates of discontinuation. Treatment should be initiated at 250 μg for the first 4 weeks and then continued at 500 μg daily.[82,83] Most experts reserve roflumilast for patients with persistent exacerbations despite triple therapy and use it cautiously for underweight patients and those with a history of depression.

Azithromycin, a macrolide antibiotic, can reduce the risk of exacerbations by 27% to 42% when taken long-term at doses of 250 mg daily or 500 mg thrice weekly.[40,84] Azithromycin has not demonstrated efficacy in patients who continue to smoke.[40] Adverse effects of chronic azithromycin include reversible hearing impairment, arrhythmias, and promotion of macrolide resistance. The authors obtain a baseline electrocardiogram to screen for QT prolongation of more than 450 milliseconds prior to initiation and monitor audiometry only if symptoms of hearing deficit present. Most experts consider azithromycin only for former smokers with persistent exacerbations despite triple therapy.

Other Pharmacologic Treatments

Long-term oral corticosteroid use is associated with adverse effects and is not appropriate for most patients with stable COPD. Theophylline does not reduce exacerbation rates and should not be generally used.[85] High-dose oral mucolytics like *N*-acetylcysteine (600 mg twice daily) may reduce exacerbations but have not been studied on patients using contemporary inhaled maintenance therapies.[86]

Specialist Referral for Advanced Treatments

Patients with COPD who continue to have unacceptable impairment in quality of life or repeated hospitalizations despite optimal pharmacological therapy and participation in pulmonary rehabilitation programs warrant specialist referral. Therapies that may be considered include bilevel noninvasive positive-pressure ventilation delivered using a face mask for chronic hypercapnic respiratory failure, lung volume reduction through surgery or bronchoscopic approaches for patients with severe emphysema and lung hyperinflation, and lung transplant evaluation in severely functionally impaired patients younger than 70 years.[87-90]

Conclusions

Chronic obstructive pulmonary disease is a complicated disease requiring intensive treatment. Appropriate use of long-acting maintenance bronchodilators, inhaled corticosteroids, and pulmonary rehabilitation decreases symptoms, optimizes functional performance, and reduces exacerbation frequency. Supplemental oxygen in patients with resting hypoxemia prolongs life, and other advanced treatments are available based on specific patient characteristics.

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