Medications for COPD: A Review of Effectiveness

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Chronic obstructive pulmonary disease (COPD) is a common problem among patients presenting to primary care. This condition has multiple individual and combined treatment regimens. The goals of treatment are to improve quality of life, exercise tolerance, sleep quality, and survival; and to reduce dyspnea, nocturnal symptoms, exacerbations, use of rescue medications, and hospitalizations. All patients benefit from bronchodilator medications as needed. Long-acting inhaled anticholinergics are probably more beneficial than short-acting formulations. Use of inhaled corticosteroids might benefit patients with mild COPD who have an inflammatory component or significant reversibility on spirometry. Patients with moderate to severe disease benefit from the use of long-acting inhaled anticholinergics, inhaled corticosteroids, and possibly a long-acting beta$_2$ agonist or mucolytics. For rescue therapy, short-acting beta$_2$ agonists or combination anticholinergics with a short-acting beta$_2$ agonist should be used. Inhaled corticosteroids should be considered before initiating a long-acting beta$_2$ agonist. Caution should be used if a long-acting beta$_2$ agonist is discontinued before initiation of an inhaled corticosteroid because this may precipitate exacerbations. Evidence to support the use of mucolytics, oral theophylline, and oral corticosteroids is limited. Patients with severe hypoxemia (i.e., arterial oxygen pressure less than 55 mm Hg or oxygen saturation less than 88 percent) should be given continuous oxygen. (Am Fam Physician 2007;76:1141-8, 1151-2.

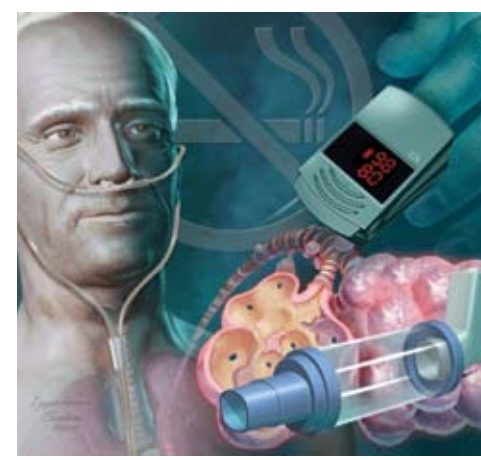

ILLUSTRATION BY BERT OPPENHEIM AND CHRIS SCALICI

▶ **Patient information:** A handout on chronic obstructive pulmonary disease, written by the authors of this article, is provided on page 1151.

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States and affects 20 percent of adults.[1,2] It is the 19th most common diagnosis made during visits to family physicians.[3] Exposure to tobacco smoke is associated with an increased lifetime risk of developing COPD,[4] and preexisting asthma is associated with a 17-fold increase in that risk.[5]

The goals of treatment for COPD are to improve quality of life, exercise tolerance, sleep quality, and survival; and to reduce dyspnea, nocturnal symptoms, exacerbations, use of rescue medications, and hospitalizations. There are multiple individual and combined treatment regimens, with options including anticholinergics, beta$_2$ agonists, smoking cessation, and steroids. This article reviews the recommendations and evidence for the pharmacologic management of stable COPD, highlighting the effect of medications on patient-oriented outcomes, such as mortality, symptoms, and hospitalization, where data exist. Information about the most commonly used medications is summarized in *Table 1*.[6-15]

Anticholinergics (Inhaled)

Inhaled short- and long-acting anticholinergics improve symptoms and quality of life in patients with COPD. There is a slightly greater benefit from the longer-acting agent tiotropium (Spiriva). One recent meta-analysis of inhaled anticholinergics found modest reductions in exacerbations, hospitalizations, and death with the use of this agent.[16] A systematic review of randomized controlled trials (RCTs) of the short-acting agent ipratropium (Atrovent) demonstrated that the drug improved patient-oriented outcomes such as exercise tolerance and sleep quality.[10] Ipratropium also has been shown to improve pulmonary function as

Table 1. Medications Commonly Used for Treating COPD: Dosage, Cost, and Adverse Effects

Medication	*Dosage*	*Cost per month**	*Serious adverse effects†*
Anticholinergics (inhaled)			
Ipratropium (Atrovent)	2 or 3 puffs three or four times daily	$77 (for 14 g; 200 inhalations)	Anaphylaxis, angioedema, bronchospasm (paradoxical), glaucoma (narrow-angle), hypersensitivity reaction, laryngospasm
Tiotropium (Spiriva)	1 cap daily	140	Angioedema, bronchospasm (paradoxical), glaucoma, hypersensitivity reaction
Beta$_2$ agonists (inhaled)			
Albuterol (Ventolin HFA)	2 to 4 puffs every 6 hours as needed	36 (for 18 g; around 200 inhalations)	Angina, angioedema, arrhythmias, bronchospasm (paradoxical), hypertension, hypokalemia, QT-interval prolongation, seizures, urticaria
Salmeterol (Serevent)	1 inhalation every 12 hours	131	Anaphylaxis, angioedema, arrhythmias, asthma exacerbation, bronchospasm (paradoxical), death (asthma-related), hypertension, laryngospasm
Corticosteroids (inhaled)			
Fluticasone (Flovent HFA; 44 to 220 mcg per puff)	88 to 440 mcg two times daily	90 (for 10.6 g; around 120 inhalations)	Adrenal suppression, anaphylactoid reactions, angioedema, behavioral disturbances (children), bronchospasm, cataracts, Churg-Strauss syndrome, Cushingoid features, eosinophilia, glaucoma, growth suppression (children), hyperglycemia, osteoporosis, vasculitis
Budesonide (Pulmicort; 90 to 180 mcg per puff)	180 to 360 mcg two times daily	177 (200 inhalations)	
Triamcinolone (Azmacort; 100 mcg per puff)	2 puffs three or four times daily	134 (for 20 g; around 240 inhalations)	
Combinations			
Inhaled anticholinergic/short-acting beta$_2$ agonist (albuterol/ipratropium [Combivent])	1 or 2 puffs four times daily as needed	100 (for 14.7 g; around 200 inhalations)	Anaphylaxis, angioedema, arrhythmias, bronchospasm (paradoxical), glaucoma (narrow-angle)
Inhaled corticosteroid/long-acting beta$_2$ agonist (fluticasone/salmeterol inhaled [Advair Diskus]: 100/50, 250/50, or 500/50 mcg per puff)	1 inhalation twice daily	210	Adrenal suppression, angioedema, arrhythmia (ventricular), asthma exacerbation, bronchospasm (paradoxical), cataracts, Churg-Strauss syndrome, cushingoid features, death (asthma-related), glaucoma, growth suppression (children), hypokalemia (severe), laryngospasm
Mucolytics			
N-acetylcysteine (Mucomyst‡)	600 mg orally two times daily	328 (4 mL 20% solution)	Anaphylaxis, bronchospasm

COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; URTI = upper respiratory tract infection; UTI = urinary tract infection.

**—Estimated cost to the pharmacist for brand-name drugs based on average wholesale prices (rounded to the nearest dollar) in Red Book. Montvale, N.J.: Medical Economics Data, 2007. Cost to the patient will be higher, depending on prescription filling fee.*

†—Information on adverse effects is taken from the Epocrates database (http://www.epocrates.com).

‡—Brand not available in the United States.

Information from references 6 through 15.

Common adverse effects†	*Comment*
COPD exacerbation, cough, dizziness, dry mouth, GI upset, headache, nausea, nervousness, oral irritation, rash, urticaria	Improves symptoms and quality of life and decreases exacerbations, hospitalizations, and deaths[6,7]
Abdominal pain, blurred vision, candidiasis, chest pain, constipation, dry mouth, dyspepsia, edema, epistaxis, infection, myalgia, pharyngitis, rash, rhinitis, tachycardia, URTI symptoms, urinary hesitancy or retention, UTI, vomiting	Improves quality of life and sleep and decreases rescue inhaler use and office visits[8-10] Higher cost
Bad taste in the mouth, cough, throat irritation, tremor, URTI symptoms	Improves breathlessness but not other patient-oriented outcomes[11]
Bronchitis, headache, nasal congestion, nervousness, palpitations, pharyngitis, rash, rhinitis, tachycardia, throat irritation, tracheitis, tremor, urticaria	Does not improve breathlessness but may decrease exacerbations (single study)[12]
Candidiasis (oral), cough, dysphonia, headache, hoarseness, pharyngitis, sinusitis, throat irritation, URTI	Decrease exacerbations in patients with moderate to severe disease[13] Maintain lowest effective dose
Bronchitis, cough, dyspnea, headache, nausea, pain, URTI	Use in patients requiring more than one bronchodilator
Bronchitis, candidiasis (oral), cough, dermatitis, diarrhea, dizziness, dyspepsia, dysphonia, headache, hoarseness, hypokalemia, nausea or vomiting, palpitations, pharyngitis, sinusitis, taste changes, throat irritation, tremor, URI	Improves lung function and quality of life and decreases exacerbations in patients with moderate to severe disease[14]
Bronchospasm, nausea, rash, rhinorrhea, stomatitis, unpleasant odor during administration, urticaria, vomiting	Small decrease in exacerbations[15]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Extended therapy with short- or long-acting inhaled anticholinergics should be used to improve symptom control and reduce exacerbations and mortality risk in patients with COPD. Long-acting agents may be slightly more beneficial than short-acting agents.	A	6-9, 16-20	Retrospective review of RCTs (NNT for long-acting over short-acting agents = 9)
Short-acting inhaled beta$_2$ agonists should be used to improve breathlessness in patients with COPD.	A	11, 12, 16, 21-23	Cochrane review of RCTs There is inconsistent evidence on the benefits of long-acting agents and some inconsistent evidence suggesting a possible increase in mortality. There is insufficient evidence that long- or short-term agents improve quality of life.
Inhaled corticosteroids should be used to reduce the frequency of COPD exacerbations, but they are not useful for symptom control.	A	13, 24	Systematic review of RCTs There is inconsistent evidence for reduction in FEV$_1$ with inhaled steroids.
High-dose oral corticosteroids may improve lung function in patients with COPD, but they have no clinically significant benefits for patient-oriented outcomes. Inhaled corticosteroids should be used instead.	A	25, 26	Cochrane review of RCTs Long-term use associated with adverse effects
Combined ipratropium and albuterol (Combivent) may be used for the treatment of bronchospasm associated with COPD in patients who require more than one bronchodilator.	B	27-29	Inconsistent evidence based on RCTs The same benefit has not been found with ipratropium (Atrovent) and salmeterol (Serevent).
Adding a long-acting beta$_2$ agonist to inhaled corticosteroid therapy provides no additional benefit over inhaled steroids alone.	B	14	Inconsistent evidence based on RCTs
Continuous supplemental oxygen should be used to improve survival in patients who have severe daytime hypoxia.	A	32	Systematic review of RCTs
Continuous supplemental oxygen may improve exercise capacity in patients with mild to moderate COPD.	B	33	Systematic review of RCTs
Use of the oral mucolytic N-acetylcysteine (Mucomyst; brand not available in the United States) provides a small reduction in exacerbations in patients with severe COPD who are not taking inhaled steroids	B	15, 31	Cochrane review of RCTs with inconsistent results
Theophylline may be considered in combination with long-acting beta$_2$ agonists in select patients with COPD.	A	34-36	Cochrane review of RCTs Adverse effects are common and monitoring is necessary.

COPD = chronic obstructive pulmonary disease; RCT = randomized controlled trial; NNT = number needed to treat; FEV$_1$ = forced expiratory volume in one second.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1095 or http://www.aafp.org/afpsort.xml.

demonstrated by a greater forced expiratory volume in one second (FEV$_1$) and forced vital capacity, especially in patients with a history of tobacco use.[6,7] Similar studies of tiotropium have shown that it improves symptom control and reduces exacerbations, rescue inhaler use, and hospitalizations.[8,9]

Several trials compared tiotropium with ipratropium and demonstrated that fewer exacerbations occurred in those receiving tiotropium.[17-20] However, it was calculated that nine patients must be treated with tiotropium rather than ipratropium for one year to prevent one exacerbation, and eight patients must be treated with tiotropium to prevent one hospitalization.[19,20] Rescue inhaler use was decreased by four uses per week with tiotropium; improved quality-of-life scores and fewer unscheduled office visits also were noted.[19,20]

The most common adverse effect in clinical trials was dry mouth, which occurred in 16 percent of patients

taking ipratropium.[17-20] This side effect was considered mild and typically resolved during the course of therapy. Additional side effects included constipation, blurred vision, glaucoma, increased heart rate, and urinary retention. The modest comparative benefits of the longer-acting agent must be balanced against its higher cost.

Beta$_2$ Agonists (Inhaled)

Short-acting rather than long-acting beta$_2$ agonists should be used to improve symptoms because they have been shown to reduce breathlessness. However, they do not affect other patient-oriented outcomes such as exercise performance. For patients with stable COPD, there is an associated improvement in FEV_1.[11]

The regular short-term use of long-acting beta$_2$ agonists did not improve breathlessness or other health-related quality-of-life measures in eight RCTs, although a small improvement in FEV_1 was found.[21] One study demonstrated that the long-acting beta$_2$ agonist salmeterol (Serevent) slightly reduced the rate of exacerbations (from 1.3 to 1.0 per year compared with placebo), but it did not improve quality of life.[12] Another study found improvements in post-dose FEV_1 but no improvement in quality of life.[22]

There is growing evidence that the use of beta$_2$-agonist therapy is not without harm and may be associated with increased cardiovascular events.[23] These events were mainly tachyarrhythmia and reduction of potassium concentrations, although there was also a trend toward more major cardiovascular events (number needed to harm over six months = 200).

Corticosteroids (Inhaled)

In patients with moderate to severe COPD, inhaled corticosteroids should be used to reduce exacerbations. A recent meta-analysis of 12 RCTs assessing inhaled corticosteroids demonstrated one fewer exacerbation for every 12 patients with moderate to severe disease who were treated for 18 months.[13] As in earlier studies, there was no effect on mortality, and the effectiveness was not significant in patients with mild disease. A previous systematic review of nine RCTs of inhaled corticosteroids used for at least six months demonstrated a significant reduction in exacerbations (number needed to treat to prevent one exacerbation over one year = 5). There was no change in all-cause mortality, but the rates of oral candidiasis and skin bruising increased.[24]

Corticosteroids (Oral)

High-dose oral steroids improve lung function by up to 20 percent in some patients when used for two to four weeks; however, a systematic review found no significant improvement in patient-oriented outcomes, and long-term use is associated with significant harm.[25] Switching from the use of oral to inhaled steroids is not associated with adverse outcomes. In one RCT involving patients with COPD who were dependent on steroids, there were no differences in disease exacerbation, quality of life, or spirometric measures when the patients switched from oral to inhaled therapy.[26]

Combinations

INHALED ANTICHOLINERGICS AND BETA$_2$ AGONISTS

Shortness of breath and wheezing can be alleviated with the use of combined ipratropium and albuterol (Combivent) administered via a metered-dose inhaler.[27,28] The same improvements have not been noted for the combination of ipratropium and salmeterol. Therefore, combined ipratropium and albuterol should be used for the treatment of bronchospasm associated with COPD in patients who require more than one bronchodilator. Patients randomized to receive ipratropium and albuterol versus albuterol alone showed greater improvement in wheezing, shortness of breath, and FEV_1.[27] When used as a nebulized treatment, this combination was not associated with the improvements seen in the metered-dose inhaler study.[28] The use of the long-acting beta$_2$ agonist salmeterol in combination with ipratropium compared with salmeterol alone only improved FEV_1; there were no significant improvements in patient-oriented outcomes.[29]

CORTICOSTEROIDS AND LONG-ACTING BETA$_2$ AGONISTS

The combination of inhaled steroids and long-acting beta$_2$ agonists reduces exacerbations, improves quality of life, and improves lung function in patients with moderate to severe COPD. In a systematic review of six RCTs, combination therapy was demonstrated to reduce exacerbations and improve quality of life compared with placebo and with beta$_2$ agonists alone, but was no more effective than steroids alone.[14] When steroids and long-acting beta$_2$ agonists were used in combination, withdrawal of the steroids resulted in an increase in exacerbations. Increased rates of oral candidiasis were reported with the steroid combinations in some trials.[30]

Mucolytics

Treatment with oral mucolytics such as N-acetylcysteine (Mucomyst; brand not available in the United States) may result in a small reduction in acute exacerbations and in the total number of days of disability for patients with moderate to severe COPD. However, the data are

conflicting. A systematic review of studies comparing oral mucolytics with placebo for three to six months showed a small decrease in exacerbations from a baseline of 2.7 exacerbations per year to 2.0 exacerbations per year with treatment.[15] This effect was greatest in patients with moderate to severe disease who were not taking inhaled corticosteroids. There were no differences in lung function or adverse effects. One recent RCT assessing N-acetylcysteine (600 mg twice daily for three years) found no difference in exacerbation rates or FEV_1.[31] Of the studied medications, only N-acetylcysteine is available in the United States; there are no RCTs available for guaifenesin (Humibid) in COPD.

Table 2. Treatment of Patients with COPD by Disease Severity

Severity of COPD	*Treatment*
Mild $FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted	Short-acting bronchodilators when needed (ipratropium [Atrovent] or albuterol [Ventolin]) Active risk-factor reduction Annual influenza immunization Pneumococcal vaccine, polyvalent (Pneumovax), if appropriate
Moderate $FEV_1/FVC < 0.70$ FEV_1 50-79% predicted	Same as for mild *and* Add one or more long-acting bronchodilator (tiotropium [Spiriva] or salmeterol [Serevent])
Severe $FEV_1/FVC < 0.70$ FEV_1 30-49% predicted	Same as for moderate *and* Add inhaled steroids Consider mucolytics
Very severe $FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $< 50\%$ predicted with chronic respiratory failure ($SaO_2 < 88$ percent)	Same as for severe *and* Long-term oxygen therapy if chronic respiratory failure

NOTE: *First counsel patients about risk reduction, management of exacerbations, and end-of-life issues, if necessary.*

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; SaO_2 = oxygen saturation.

Information from reference 2.

Oxygen (Long-term)

Continuous supplemental oxygen should be used to improve exercise performance and survival in patients with moderate to severe COPD who have severe daytime hypoxemia (arterial oxygen pressure less than 55 mm Hg or oxygen saturation [SaO_2] less than 88 percent). There also is evidence for improvement in endurance and exercise capacity with supplemental oxygen. There is no improvement in mortality when oxygen is used for patients with mild hypoxemia or nocturnal hypoxemia alone. One systematic review of RCTs found that continuous supplemental oxygen improved survival compared with nocturnal oxygen or no oxygen when used for 24 months in patients with an SaO_2 less than 88 percent.[32] Similarly, a Cochrane review identified 27 RCTs that showed better endurance and exercise capacity with the use of supplemental oxygen in participants who had moderate to severe COPD.[33] However, the individual trials had small sample sizes, and there may have been publication bias.

Theophylline

Treatment with theophylline may cause a small improvement in FEV_1; however, it is poorly tolerated, requires monitoring, and does not improve patient-oriented outcomes such as breathlessness. A systematic review of 20 RCTs ranging from one week to three months in duration found no difference in symptoms with theophylline.[34]

Theophylline may be useful as adjunctive therapy in combination with long-acting $beta_2$ agonists in carefully selected patients. One trial comparing salmeterol, oral theophylline, and a combination of both in patients with moderate to severe COPD showed that the combination was more effective than either drug alone and that salmeterol was more effective than theophylline alone.[35] Patients taking the combination therapy had fewer exacerbations, improved symptom scores, and improved FEV_1. Gastrointestinal side effects were more common with theophylline. An additional comparison of theophylline and long-acting $beta_2$ agonists demonstrated superiority of the long-acting $beta_2$ agonists over theophylline in patient-oriented outcomes and physiologic measures, and again showed the lack of benefit with theophylline in quality of life and in exacerbation occurrence.[36]

Approach to the Patient

Patients at risk of COPD, but with normal results on spirometry, should receive education about risk reduction and influenza vaccination. In patients with COPD, patient education is paramount and should focus on smoking cessation, reduction of occupational and environmental exposures, management of exacerbations, and end-of-life issues.[2]

The pharmacologic approach is based on the stage of illness *(Table 2[2])*.[37] In patients with mild disease, the use of short-acting bronchodilators as needed is appropriate. With progression to moderate disease, one or more long-acting bronchodilators should be added. Progression to

severe disease warrants the addition of inhaled steroids, and patients with multiple exacerbations should be given mucolytics. Patients with end-stage disease and hypoxia should be given long-term oxygen therapy. Some patients have a response with theophylline use, but for most patients the risks outweigh the benefits.

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Author disclosure: Nothing to disclose.

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