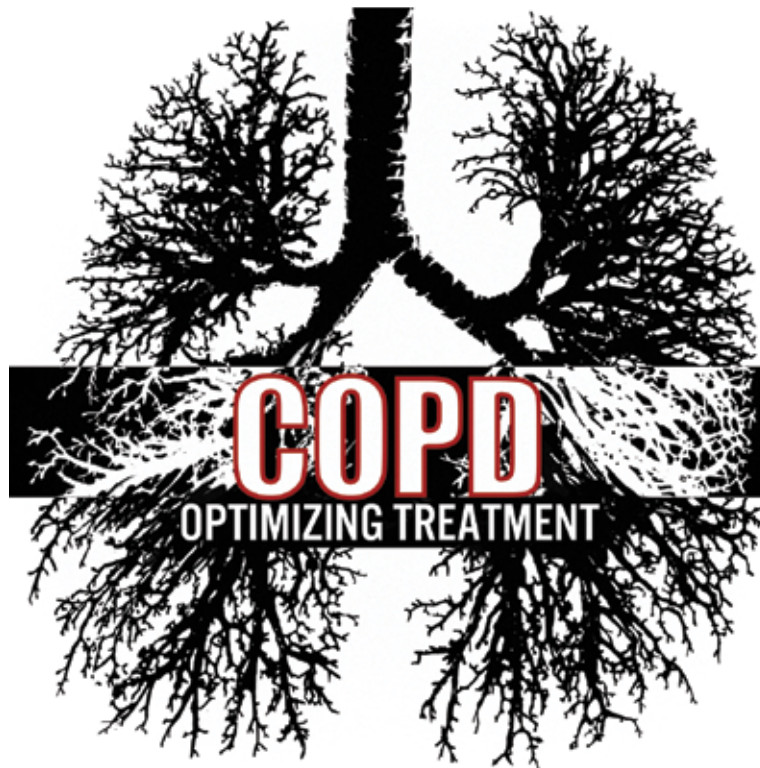


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A guideline update and an expanded armamentarium have many physicians wondering how best to treat patients with COPD. Here's help.

PRACTICE RECOMMENDATIONS

› *Individualize treatment regimens based on severity of symptoms and risk for exacerbation, prescribing short-acting beta₂-agonists, as needed, for all patients with chronic obstructive pulmonary disease (COPD). (A)*

› *Limit use of inhaled long-acting beta₂-agonists to the recommended dosage; higher doses do not lead to better outcomes. (A)*

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

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Chronic obstructive pulmonary disease (COPD) carries a high disease burden. In 2012, it was the 4th leading cause of death worldwide.^{1,2} In 2015, the World Health Organization updated its Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, classifying patients with COPD based on disease burden as determined by symptoms, airflow obstruction, and exacerbation history.³ These revisions, coupled with expanded therapeutic options within established classes of medications and new combination drugs to treat COPD (TABLE 1),³⁻⁶ have led to questions about interclass differences and the best treatment regimen for particular patients.

Comparisons of various agents within a therapeutic class and their impact on lung function and rate of exacerbations address many of these concerns. In the text and tables that follow, we present the latest evidence highlighting differences in dosing, safety, and efficacy. We also include the updated GOLD classifications, evidence of efficacy for pulmonary rehabilitation, and practical implications of these findings for the optimal management of patients with COPD.

But first, a word about terminology.

Understanding COPD

COPD is a chronic lung disease characterized by progressive airflow limitation, usually measured by spirometry (TABLE 2),³ and chronic airway inflammation. Emphysema and chronic bronchitis are often used synonymously with COPD. In fact, there are important differences.

Individuals with chronic bronchitis do not necessarily have the airflow limitations found in those with COPD. And patients with COPD develop pathologic lung changes beyond the alveolar damage characteristic of emphysema, including airway fibrosis and inflammation, luminal plugging, and loss of elastic recoil.³

The medications included in this review aim to reduce both the morbidity and mortality associated with COPD. These drugs can also help relieve the symptoms of patients with chronic bronchitis and emphysema, but have limited effect on patient mortality.

Short- and long-acting beta₂-agonists

Bronchodilator therapy with beta₂-agonists improves forced expiratory volume in one second (FEV₁) through relaxation of airway smooth muscle. Beta₂-agonists have proven to be safe and effective when used as needed or scheduled for patients with COPD.⁷

Inhaled short-acting beta₂-agonists (SABAs) improve FEV₁ and symptoms within 10 minutes, with effects lasting up to 4 to 6 hours; long-acting beta₂-agonists (LABAs) have a variable onset, with effects lasting 12 to 24 hours.⁸ Inhaled levalbuterol, the last SABA to receive US Food and Drug Administration approval, has not proven to be superior to conventional bronchodilators in ambulatory patients with stable COPD.³ In clinical trials, however, the slightly longer half-life of the nebulized formulation of levalbuterol was found to reduce both the frequency of administration and the overall cost of therapy in patients hospitalized with acute exacerbations of COPD.^{9,10}

Recently approved LABAs

Clinical trials have studied the safety and efficacy of newer agents vs older LABAs in

patients with moderate to severe COPD. Compared with theophylline, for example, formoterol 12 mcg inhaled every 12 hours for a 12-month period provided a clinically significant increase of >120 ml in FEV₁ ($P=.026$).¹¹ Higher doses of formoterol did not provide any additional improvement.

In a trial comparing indacaterol and tiotropium, an inhaled anticholinergic, both treatment groups had a clinically significant increase in FEV₁, but patients receiving indacaterol achieved an additional increase of 40 to 50 mL at 12 weeks.¹²

Exacerbation rates for all LABAs range from 22% to 44%.^{5,12,13} In a study of patients receiving formoterol 12 mcg compared with 15-mcg and 25-mcg doses of arformoterol, those taking formoterol had a lower exacerbation rate than those on either strength of arformoterol (22% vs 32% and 31%, respectively).¹⁰ In various studies, doses greater than the FDA-approved regimens for indacaterol, arformoterol, and olodaterol did not result in a significant improvement in either FEV₁ or exacerbation rates compared with placebo.^{5,12,14}

Studies that assessed the use of rescue medication as well as exacerbation rates in patients taking LABAs reported reductions in the use of the rescue drugs ranging from 0.46 to 1.32 actuations per day, but the findings had limited clinical relevance.^{5,13} With the exception of indacaterol and olodaterol—both of which may be preferable because of their once-daily dosing regimen—no significant differences in safety and efficacy among LABAs have been found.^{5,12,13}

Long-acting inhaled anticholinergics

Inhaled anticholinergic agents (IACs) can be used in place of, or in conjunction with, LABAs to provide bronchodilation for up to 24 hours.³ The introduction of long-acting IACs dosed once or twice daily has the potential to improve medication adherence over traditional short-acting ipratropium, which requires multiple daily doses for symptom control. Over 4 years, tiotropium has been shown to increase time to first exacerbation by approximately 4 months. It did not, how-

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Exacerbation rates for all long-acting beta₂-agonists range from 22% to 44%.

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TABLE 1

COPD: Assessing newer inhaled treatments³⁻⁶

Drug/dose (trade name)	Dosing frequency (hours)	Evidence
LABAs		
Arformoterol 15 mcg/2 mL solution for nebulization (Brovana)	12	Evidence level not assessed in current guidelines Nebulized arformoterol MDI resulted in a clinically significant higher % change in FEV ₁ vs salmeterol Slightly higher exacerbation rates with arformoterol than with formoterol
Indacaterol DPI 75 mcg (Arcapta Neohaler)	24	Bronchodilator effect greater than salmeterol and formoterol; similar to tiotropium Decreases breathlessness and exacerbations, improves overall health status
Long-acting IACs		
Acclidinium bromide 400 mcg DPI (Tudorza Pressair)	12	Evidence level not determined in current guidelines, but statement notes that acclidinium is similar to tiotropium for lung function and shortness of breath
Tiotropium 17 mcg DPI (Spiriva Handihaler)	24	Reduces exacerbations and hospitalizations, improves symptoms and effectiveness of pulmonary rehabilitation
Umeclidinium bromide 62.5 mcg DPI (Incruse Ellipta)	24	Not assessed in current guidelines; active comparator trials pending Compared with placebo, umeclidinium resulted in clinically significant improvements in FEV ₁
Combinations		
ICS + LABA Fluticasone + vilanterol 100/25 DPI (Breo Ellipta)	24	ICS + a LABA or long-acting IAC is more effective than individual components in improving lung function and health status in patients with moderate to very severe COPD Combination therapy is associated with an increased risk of pneumonia, but with no other significant adverse effects
LABA + IAC Umeclidinium + vilanterol 62.5/25 DPI (Anoro Ellipta)	24	Not assessed in current guidelines Product improved lung function vs monotherapy with vilanterol

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; IAC, inhaled anticholinergic agent; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; MDI, metered dose inhaler (aerosol).

ever, significantly reduce the number of exacerbations compared with placebo.¹⁵

Long-term use of tiotropium appears to have the *potential* to preserve lung function. In one trial, it slowed the rate of decline in FEV₁ by 5 mL per year, but this finding lacked clinical significance.¹³ In clinical trials of pa-

tients with moderate to severe COPD, however, once-daily tiotropium and umeclidinium provided clinically significant improvements in FEV₁ (>120 mL; $P < .01$), regardless of the dose administered.^{6,16} In another trial, patients taking acclidinium 200 mcg or 400 mcg every 12 hours did not achieve a clinically sig-



Long-acting inhaled anticholinergic agents—when used in combination with LABAs—have a positive effect on FEV₁, but their effect on exacerbation rates has not been established.

TABLE 2

GOLD classification of severity of airflow limitations³

In patients with FEV ₁ /FVC <0.70		
Class 1	Mild	FEV ₁ ≥80% predicted
Class 2	Moderate	FEV ₁ ≥50% to <80% predicted
Class 3	Severe	FEV ₁ ≥30% to <50% predicted
Class 4	Very severe	FEV ₁ <30% predicted

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

nificant improvement in FEV₁ compared with placebo.¹⁷

In patients with moderate to severe COPD, the combination of umeclidinium/vilanterol, a LABA, administered once daily resulted in a clinically significant improvement in FEV₁ (167 mL; *P*<.001) vs placebo—but was not significantly better than treatment with either agent alone.¹⁸

Few studies have evaluated time to exacerbation in patients receiving aclidinium or umeclidinium. In comparison to salmeterol, tiotropium reduced the time to first exacerbation by 42 days at one year (hazard ratio=0.83; 95% confidence interval [CI], 0.77-0.9; *P*<.001).¹⁹ The evidence suggests that when used in combination with LABAs, long-acting IACs have a positive impact on FEV₁, but their effect on exacerbation rates has not been established.

Combination therapy with steroids and LABAs

The combination of inhaled corticosteroids (ICS) and LABAs has been found to improve FEV₁ and symptoms in patients with moderate to severe COPD more than monotherapy with either drug class.^{20,21} In fact, ICS alone have not been proven to slow the progression of the disease or to lower mortality rates in patients with COPD.²²

Fluticasone/salmeterol demonstrated a 25% reduction in exacerbation rates compared with placebo (*P*<.0001), a greater reduction than that of either drug alone.²⁰ A retrospective observational study comparing fixed dose fluticasone/salmeterol with

budesonide/formoterol reported a similar reduction in exacerbation rates, but the number of patients requiring the addition of an IAC was 16% lower in the latter group.²³

The combination of fluticasone/vilanterol has the potential to improve adherence, given that it is dosed once daily, unlike other COPD combination drugs. Its clinical efficacy is comparable to that of fluticasone/salmeterol after 12 weeks of therapy, with similar improvements in FEV₁,²⁴ but fluticasone/vilanterol is associated with an increased risk of pneumonia.³

Chronic use of oral corticosteroids

Oral corticosteroids (OCS) are clinically indicated in individuals whose symptoms continue despite optimal therapy with inhaled agents that have demonstrated efficacy. Such patients are often referred to as “steroid dependent.”

While OCS are prescribed for both their anti-inflammatory activity and their ability to slow the progression of COPD,^{25,26} no well-designed studies have investigated their benefits for this patient population. One study concluded that patients who were slowly withdrawn from their OCS regimen had no more frequent exacerbations than those who maintained chronic usage. The withdrawal group did, however, lose weight.²⁷

GOLD guidelines do not recommend OCS for chronic management of COPD due to the risk of toxicity.³ The well-established adverse effects of chronic OCS include hyperglycemia, hypertension, osteoporosis, and myopathy.^{28,29} A study of muscle function in 21 COPD patients receiving corticosteroids revealed decreases in quadriceps muscle strength and pulmonary function.³⁰ Daily use

TABLE 3

Recommended therapies based on GOLD classification³

Category	Characteristics	First-line therapies
A (Class 1 and 2)	Low risk, <i>less</i> symptoms	Pulmonary rehabilitation <i>and</i> short-acting IAC <i>or</i> SABA
B (Class 1 and 2)	Low risk, <i>more</i> symptoms	Therapies for category A <i>and</i> long-acting IAC <i>or</i> LABA
C (Class 3 and 4)	High risk, <i>less</i> symptoms	Therapies for category A <i>and</i> ICS + LABA <i>or</i> long-acting IAC
D (Class 3 and 4)	High risk, <i>more</i> symptoms	Therapies for category A <i>and</i> ICS + LABA <i>and/or</i> long-acting IAC <i>and/or</i> PDE-4 inhibitor

GOLD, Global Initiative for Chronic Obstructive Lung Disease; IAC, inhaled anticholinergic; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; PDE-4, phosphodiesterase-4; SABA, short-acting beta₂-agonist.



In one study, patients slowly withdrawn from oral corticosteroids had no more frequent exacerbations than those who maintained chronic usage.

of OCS will likely result in additional therapies to control drug-induced conditions, as well—another antihypertensive secondary to fluid retention caused by chronic use of OCS in patients with high blood pressure, for example, or additional medication to control elevated blood glucose levels in patients with diabetes.

Phosphodiesterase-4 inhibitors

The recommendation for roflumilast in patients with GOLD Class 2 to 4 symptoms remains unchanged since the introduction of this agent as a treatment option for COPD.³ Phosphodiesterase-4 (PDE-4) inhibitors such as roflumilast reduce inflammation in the lungs

and have no activity as a bronchodilator.^{31,32}

Roflumilast has been shown to improve FEV₁ in patients concurrently receiving a long-acting bronchodilator and to reduce exacerbations in steroid-dependent patients, a recent systematic review of 29 PDE-4 trials found.³³ Patients taking roflumilast, however, suffered from more adverse events (nausea, appetite reduction, diarrhea, weight loss, sleep disturbances, and headache) than those on placebo.³³

Antibiotics

GOLD guidelines do not recommend the use of antibiotics for patients with COPD, except

➤ **Patients with limited mobility can benefit from non-exercise components of pulmonary rehabilitation.**

to treat acute exacerbations.¹ However, recent studies suggest that routine or pulsed dosing of prophylactic antibiotics can reduce the number of exacerbations.³⁴⁻³⁶ A 2013 review of 7 studies determined that continuous antibiotics, particularly macrolides, reduced the number of COPD exacerbations in patients with a mean age of 66 years (odds ratio [OR]=0.55; 95% CI, 0.39-0.77).³⁷

A more recent trial randomized 92 patients with a history of ≥ 3 exacerbations in the previous year to receive either prophylactic azithromycin or placebo daily for 12 months. The treatment group experienced a significant decrease in the number of exacerbations (OR=0.58; 95% CI, 0.42-0.79; $P=.001$).³⁸ This benefit must be weighed against the potential development of antibiotic resistance and adverse effects, so careful patient selection is important.

Pulmonary rehabilitation has proven benefits

GOLD, the American College of Chest Physicians, the American Thoracic Society, and the European Respiratory Society all recommend pulmonary rehabilitation for patients with COPD.³⁹⁻⁴¹ In addition to reducing morbidity and mortality rates—including a reduction in number of hospitalizations and length of stay and improved post-discharge recovery—pulmonary rehabilitation has been shown to have other physical and psychological benefits.⁴² Specific benefits include improved exercise capacity, greater arm strength and endurance, reduced perception of intensity of breathlessness, and improved overall health-related quality of life.

Key features of rehab programs

Important components of pulmonary rehabilitation include counseling on tobacco cessation, nutrition, education—including correct inhalation technique—and exercise training. There are few contraindications to participation, and patients can derive benefit from both its non-exercise components and upper extremity training regardless of their mobility level.

A 2006 Cochrane review concluded that an effective pulmonary rehabilitation pro-

gram should be at least 4 weeks in duration,⁴³ and longer programs have been shown to produce greater benefits.⁴⁴ However, there is no agreement on an optimal time frame. Studies are inconclusive on other specific aspects of pulmonary rehab programs, as well, such as the number of sessions per week, number of hours per session, duration and intensity of exercise regimens, and staff-to-patient ratios.

■ **Home-based exercise training** may produce many of the same benefits as a formal pulmonary rehabilitation program. A systematic review found improved quality of life and exercise capacity associated with patient care that lacked formal pulmonary rehabilitation, with no differences between results from home-based training and hospital-based outpatient pulmonary rehabilitation programs.⁴⁵

Given the lack of availability of formal rehab programs in many communities, home-based training for patients with COPD is important to consider.

Implications for practice

What is the takeaway from this evidence-based review? Overall, it is clear that, with the possible exception of the effect of once-daily dosing on adherence, there is little difference among the therapeutic agents within a particular class of medications—and that more is not necessarily better. Indeed, evidence suggests that higher doses of LABAs may reduce their effectiveness, rendering them no better than placebo. In addition, there is no significant difference in the rate of exacerbations in patients taking ICS/LABA combinations and those receiving IACs alone.

Pulmonary rehabilitation should be recommended for all newly diagnosed patients, while appropriate drug therapies should be individualized based on the GOLD symptoms/risk evaluation categories (TABLE 3).³ While daily OCS and daily antibiotics have the potential to reduce exacerbation rates, for example, the risks of adverse effects and toxicities outweigh the benefits for patients whose condition is stable.

Determining the optimal treatment for a particular patient also requires an assess-

TABLE 4

Adverse effects to consider in treatment selection

Medication class	Common adverse effects	Clinical impact
Inhaled beta ₂ -agonists	Tachycardia, dyspepsia, nausea, nervousness, insomnia, tremor ^{46,47}	Adverse effects more pronounced with SABAs vs LABAs ^{46,47} Inhaled anticholinergics may be an appropriate alternative to inhaled beta ₂ -agonists for patients with a history of anxiety, arrhythmias, dilated cardiomyopathy, ischemic heart disease, insomnia, or gastric reflux ³ May be less effective in patients on non-selective beta-blockers ³
Inhaled anticholinergics	Dry mouth ⁴⁸	Poor systemic absorption following inhalation ⁴⁸ May be preferable to inhaled beta ₂ -agonists for elderly patients or those with multiple comorbidities due to safety profile ^{3,49} Combination of inhaled anticholinergics and smaller doses of beta ₂ -agonists provide improvements in FEV ₁ with fewer systemic adverse effects ³
Inhaled corticosteroids	Oral candidiasis and pneumonia ⁵⁰	Immunocompromised patients and those with uncontrolled diabetes are at higher risk ⁵⁰ Counseling on proper administration technique may prevent adverse effects
Continuous antibiotics	GI distress (nausea, vomiting, diarrhea) ⁵¹ Antibiotic resistance ⁵¹	Crohn's disease, IBS, and other conditions affecting GI motility may be exacerbated with chronic use of macrolide antibiotics ⁵¹ Development of antibiotic resistance limits choice of antimicrobials for acute infections
Oral corticosteroids (daily)	Hyperglycemia, hypertension, reduced bone mineral density, and muscle weakness ^{3,27-29}	Well established relationship with multiple chronic conditions that significantly impact morbidity and mortality ³ Daily oral corticosteroid use will likely result in additional therapies to control drug-induced conditions ³
PDE-4 inhibitors	GI discomfort, headache, worsening depression, and weight loss ^{33,52}	Most common adverse effects are transient ⁵² Depression is a common comorbid condition in patients with COPD. Pulmonary rehabilitation has been determined to improve symptoms of disease-associated depression and should be considered along with pharmacotherapy for depression in patients receiving PDE-4 inhibitors ³ PDE-4 inhibitor use is associated with weight loss; functional status and stability should be assessed frequently to reduce the risk of falls ^{3,49}

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; GI, gastrointestinal; IBS, irritable bowel syndrome; LABAs, long-acting beta₂-agonists; PDE-4, phosphodiesterase-4; SABAs, short-acting beta₂-agonists.



An effective pulmonary rehabilitation program should be at least 4 weeks long.

ment of comorbidities, including potential adverse drug effects (TABLE 4).^{3,27-29,33,46-52} Selection of medication should be driven by patient and physician preference to optimize adherence and clinical outcomes, although cost and accessibility often play a significant role, as well. **JFP**

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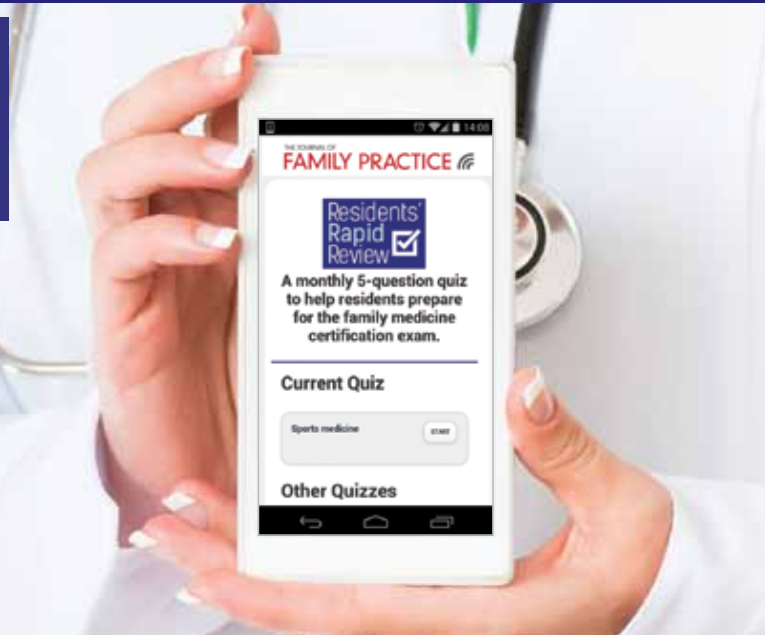
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