

GUIDELINE UPDATE

GOLD Global Strategy for the Diagnosis, Management, and Prevention of COPD

FOCUS ON PHARMACOLOGIC TREATMENT FOR COPD

APRIL 2017

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With updated assessment tool and pharmacologic treatment algorithms, LAMA/LABA therapy takes central role in recommendations for the treatment of COPD.

Guideline Overview

Comprehensive revision to previous pharmacologic and non-pharmacologic therapies for treatment of COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) released its 2017 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (COPD) as a statement of evidence and consensus for accepted treatment approaches for COPD.

COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. Emphysema and chronic bronchitis are not included in the definition of COPD because chronic respiratory symptoms may precede the development of airflow limitation and may be associated with the development of acute respiratory events.

It is the fourth leading cause of death globally, and it is expected to be the third leading cause of death by 2020, worldwide.

COPD also presents significant economic and social burdens globally. In the United States, the direct and indirect costs of COPD are estimated at \$32 billion and \$20.4 billion, respectively. In terms of Disability-Adjusted Life Years (DALY)—which is a composite measure of the burden of health problems to estimate the percentage of mortality and disability attributed to diseases and injuries—COPD contributes significantly to sum years lost; in the United States, COPD is the second leading cause of diminished DALYs.

“COPD represents an important public health challenge that is both preventable and treatable,” report authors write. “[It is] a major cause of chronic morbidity and mortality throughout the world; many people suffer from this disease for years, and die prematurely from it or its complications.” For this reason, the 2017 GOLD report provides improved strategies for the diagnosis and management of COPD.

The 2017 report acts as an update to the 2011 GOLD consensus report and subsequent updates in January 2013, 2014, 2015, and 2016, which maintained the same assessment and treatment paradigms outlined in 2011. The 2017 report provides refinements of previous COPD assessment tools. The Gold Science Committee members also conducted an extensive review of the most current literature, providing evidence-based recommendations in a four-level scheme:

- Evidence A: randomized control trials (RCTs); rich body of high-quality evidence without any significant limitation or bias
- Evidence B: RCTs with important limitations; limited body of evidence
- Evidence C: non-randomized trials; observational studies
- Evidence D: panel consensus judgment

The literature review resulted in the “comprehensive revision and reassessment of the recommendations for the various pharmacologic and non-pharmacologic therapies for COPD.”

The overall goals for the treatment of stable COPD are two-fold: reduce the symptoms and reduce the risk. Clini-

cians should seek to improve overall exercise tolerance and health status while preventing disease progression, preventing and treating exacerbations, and reducing mortality.

In this newsletter, we provide a summary of key guideline updates for the treatment of COPD, with a focus on the pharmacological treatment recommendations.

Diagnosis and Assessment

Diagnosis

The key markers of COPD are persistent respiratory symptoms and airflow limitations due to airway and/or alveolar abnormalities.

The report notes that COPD is caused by a “complex interplay of long-term cumulative exposure to noxious gases and particles, combined with a variety of host factors, including genetics, airway hyper-responsiveness and poor lung growth during childhood.” Any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease, should be evaluated for COPD. See **TABLE 1** for other key indicators for considering a diagnosis of COPD.

TABLE 1 Key indicators for considering a diagnosis of COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.

Dyspnea that is: Progressive over time. Characteristically worse with exercise. Persistent.

Chronic cough: May be intermittent and may be unproductive. Recurrent wheeze.

Chronic sputum production: Any pattern of chronic sputum production may indicate COPD.

History or risk factors: Host factors such as genetic factors, congenital/development abnormalities, etc. Tobacco smoke (including popular local preparations). Smoke from home cooking and heating fuels. Occupational dusts, vapors, fumes, gases, and other chemicals.

Family history of COPD and/or childhood factors: For example, low birthweight, childhood respiratory infections, etc.

To make a diagnosis of COPD, spirometry—the most reproducible and objective measurement of airflow limitation—should be used. Spirometry measurements are evaluated against appropriate reference values based on age, height, sex, and weight. A post-bronchodilator measurement of $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and, therefore, COPD in patients with correlating symptoms and risk factors. (See the full 2017 Global Strategy for the Diagnosis, Management, and Prevention of COPD report for considerations in performing and evaluating spirometry measurements.)

Assessment

In order to determine best therapy, COPD should be assessed to establish the level of airflow limitation, its impact on a patient’s health, and the risk of further exacerbations, hospital admissions, and/or death.

Assessment should consider four factors of the disease, independently of each other:

- **The presence and severity of the spirometric abnormality**, classified in a four-level grading system by airflow limitation severity (GOLD 1 - 4) (See **FIGURE 1**).
- **Current nature and magnitude of a patient’s symptoms**, typically measured via questionnaire—such as the COPD Assessment Test (CAT™) and The COPD Control Questionnaire (The CCQ©)—which offer patient-reported health status (factors such as breathlessness and ability to engage in physical activities).
- **Exacerbation history and future risk**, defined as an acute worsening of respiratory symptoms that result in additional therapy; events are classified as mild (treated with short-acting bronchodilators [SABDs] only), moderate (treated with SABDs plus antibiotics and/or oral corticosteroids), or severe (patient requires hospitalization or visits to the emergency department).

FIGURE 1 Refined GOLD ABCD assessment tool

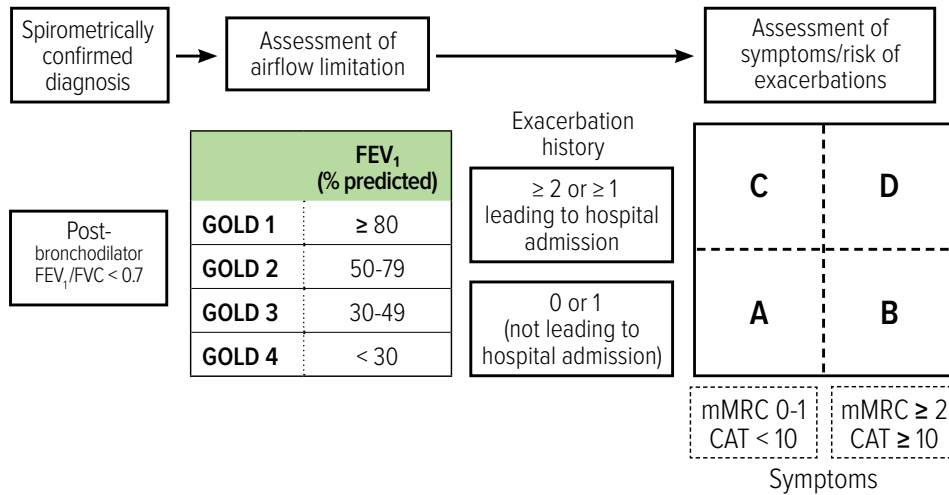
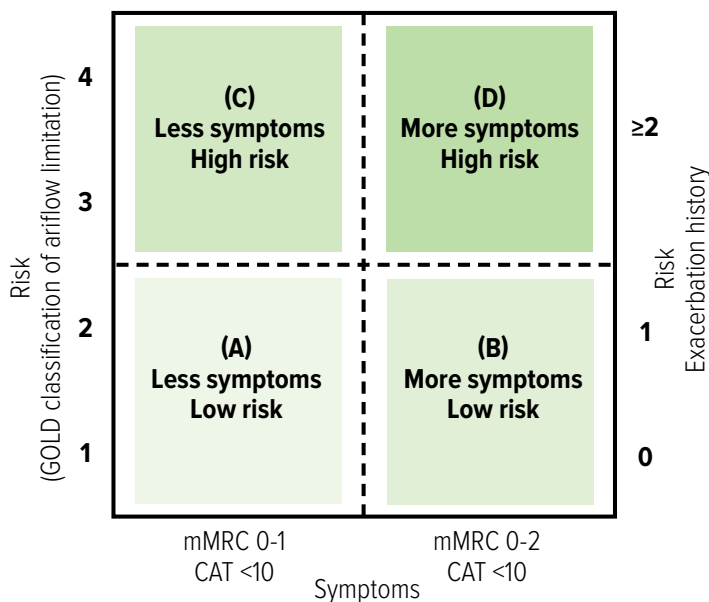


FIGURE 2 GOLD ABCD assessment tool



- **Presence of comorbidities**, such as cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer.

Revised Combined COPD Assessment Tool

The 2017 report provides an updated assessment tool toward the end of establishing the best therapeutic approaches for patients with COPD.

Currently, assessment combines the spirometric grading

system (FIGURE 1) with the “ABCD” assessment tool of the 2011 GOLD update (FIGURE 2).

While this assessment strategy integrates multimodality assessment, symptom burden, and emphasizes the importance of exacerbation prevention in the management of COPD, the Gold Science Committee members have provided a refinement of the ABCD assessment tool (FIGURE 1).

Whereas the previous assessment strategy combined the spirometric grading system with the ABCD assessment tool, ABCD groups will now be derived exclusively from patient symptoms and their history of exacerbation. Spirometry, in conjunction with patient symptoms and exacerbation history, is still critical for the diagnosis, prognostication, and consideration of other important therapeutic approaches. Again, while the spirometry number (Grade 1-4) provides indication of the severity of airflow limitation, the letter (groups

A to D) represents symptom burden and risk of exacerbation, which can be used to guide pharmacotherapeutic approaches.

“The ability to assess patients based on symptoms and exacerbation history, independent of spirometric value, allows clinicians to initiate a treatment plan based on the revised ABCD scheme alone,” report authors write. “This assessment approach acknowledges the limitations of FEV₁ in making treatment decisions for individual patient care and highlights the importance of patient symptoms and exacerbation risks in guiding therapies in COPD.”

Pharmacologic Therapy for Stable COPD Overview

Key Update

- LABA/ICS is not recommended for any patients as first-line treatment (FIGURE 3)
- LAMA/LABA therapy is now the preferred treatment option for patients in GOLD Group B-D, including first-line treatment of symptomatic COPD patients, regardless of exacerbation risk (FIGURE 3)

Pharmacologic therapy for COPD works to diminish symptoms, decrease the frequency and severity of exacerbations, and progress exercise tolerance and health status.

“Each pharmacologic treatment should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient’s response, preference and ability to use various drug delivery devices,” report authors write.

Classes of Medications for the Treatment of COPD

- **Bronchodilators**—Increase FEV₁ and/or change other spirometric variables. They work by altering airway smooth muscle tone and the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Bronchodilator medications in COPD are most often given on a regular basis to prevent or reduce symptoms.
 - » **Beta₂-agonists.** The principal action of beta₂-agonists is to relax airway muscle by stimulating beta₂-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. There are short-acting (SABA) and long-acting (LABA) beta₂-agonists. SABAs typically wear off within 4-6 hours, and LABAs show a duration of action of 12 or more hours.
- **Antimuscarinic drugs**—Block the bronchoconstriction effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle. Short-acting antimuscarinics (SAMAS), block the inhibitory neuronal receptor M2, which can cause vagally induced bronchoconstriction. Long-acting antimuscarinics (LAMAs) have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of the bronchodilator effect.
- **Methylxanthines**—May act as non-selective phosphodiesterase inhibitors, and have also been reported to have a range of non-bronchodilator actions—the significance of which has been disputed.
- **Combination bronchodilator therapy**—Bronchodilators are combined with different mechanisms and durations of action to increase the degree of bronchodilation with lower risk of side-effects compared to increasing the dose of a single bronchodilator. There are, for example, numerous combinations of LABA and LAMA in a single inhaler available; these combinations have shown to improve lung function compared to placebo. One study in patients with a history of exacerbations confirmed that a LABA/LAMA decreased exacerbations to a greater extent than an inhaled corticosteroids (ICS)/LABA combination.
- **ICS**—*In vitro* evidence suggests that COPD-associated inflammation has limited responsiveness to corticosteroids. Some drugs—such as beta₂-agonists—may partially facilitate corticosteroid sensitivity. *In vivo* data suggests that the dose-response relation and long-term (> 3 years) safety of ICS in patients with COPD are unclear and require further investigation.
- **Triple inhaled therapy**—A step up in inhaled treatment to LABA plus LAMA plus ICS. Adding a LAMA to existing LABA/ICS improves lung function and patient-reported outcomes, though a RCT did not demonstrate benefit of adding ICS to LABA plus LAMA on exacerbations. Overall, more evidence is needed to draw conclusions on the benefits of triple therapy LABA/LAMA/ICS compared to LABA/LAMA.
- **Oral glucocorticoids**—Used in the acute management of exacerbations of COPD, but are not used in the chronic daily treatment in COPD because of the lack of benefit balanced against a significant rate of systemic complications, such as muscle weakness, decreased functionality, and respiratory failure in patients with very severe COPD.
- **Phosphodiesterase-4 (PDE4) inhibitors**—Reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. Roflumilast—a once-daily oral medication

with no bronchodilator activity—reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD, and a history exacerbations. The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators.

- **Antibiotics**—Shown to have little clinical benefit in reducing exacerbations when taken continuously. Azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (500 mg two times per day) for one year in patients prone to exacerbations reduced the risk of exacerbations compared to usual care. There are no data beyond one year showing the efficacy or safety of chronic antibiotic use to prevent COPD exacerbations.
- **Mucolytic and antioxidant agents**—Given to COPD patients not receiving ICS treatment. Mucolytic may reduce exacerbations and modestly improve health status. However, available data do not identify precisely the potential target population for antioxidant agents in COPD.

- **Other drugs with anti-inflammatory potential**—

- » **Immunoregulators** have been shown to decrease severity and frequency of exacerbations, though more studies are needed to show the long-term effects of this therapy in patients receiving recommended COPD maintenance therapy.
- » **Anti-TNF-alpha antibody** (infliximab) showed no evidence of benefit, and some evidence of harm, in patients with moderate to severe COPD.
- » **Simvastatin** has not shown to prevent exacerbations in patients with COPD who had no metabolic or cardiovascular indications for statin treatment.
- » **Vitamin D** supplementation has not shown to have a positive impact on exacerbations in unselected patients.

Current and Updated Pharmacological Treatment Recommendations for Stable COPD

LAMA/LABA central to new recommendations for the pharmacologic treatment of COPD

For pharmacologic treatment, each treatment regimen should be tailored to each patient as the relationship between severity of symptoms, airflow limitation, and severity of exacerbation can differ between patients. The refined ABCD assessment tool (FIGURE 1) guides clinicians in developing a more individualized approach as each category (groups A-D) has its own treatment algorithm.

Key Points for the Inhalation of Drugs

- The choice of inhaler should be individually tailored depending on access, cost, prescriber, patient's ability, and preferences.
- Instructions and a demonstration for proper inhalation technique should accompany prescription; technique should be re-checked at each visit with patients on continued inhaler use.
- Inhaler technique (and adherence to therapy) should be assessed before determining that current therapy requires modification.

Key Points for the Use of Bronchodilators

- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (Evidence A).
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. Patients with persistent dyspnea on one bronchodilator treatment should be escalated to two (Evidence A).
- Inhaled bronchodilators are recommended over oral bronchodilators (Evidence A).

Key Points for the Use of Anti-inflammatory Agents

- Long-term monotherapy with ICS is not recommended (Evidence A).
 - » Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators (Evidence A).
 - » Long-term therapy with oral corticosteroids is not recommended (Evidence A).
 - » In patients with exacerbations despite LABA/ICS or LABA/LAMA/ICS, chronic bronchitis and severe to very severe airflow obstruction, the addition of a PDE4 inhibitor can be considered (Evidence B).
- » In former smokers with exacerbations despite appropriate therapy, macrolides can be considered (Evidence B).
- » Statin therapy is not recommended for prevention of exacerbations (Evidence A).
- » Antioxidant mucolytics are recommended only in selected patients (Evidence A).

Pharmacologic Treatment Algorithms

Treatment escalation now reported

FIGURE 3 shows the preferred treatment pathways by GOLD Grade, which includes a proposed model for the initiation, and then subsequent escalation and/or de-escalation of pharmacologic management of COPD according to the individualized assessment of symptoms.

Previous GOLD reports only provided recommendations for initial therapy; the recommendations offered in **FIGURE 3** are based on availability of efficacy and safety data. Report authors note that treatment escalation has not been systematically tested and that trials of de-escalation are also limited and only include ICS.

Report authors provide supplemental rationale for certain recommendations in **FIGURE 3** made for Group C and Group D:

Group B

- A long-acting bronchodilator should be used for initial therapy as they are “superior” to short-acting bronchodilators; two bronchodilators may be considered as initial therapy for patients with severe breathlessness (stepped down to single if two does not improve symptoms).
- The choice of class of long-acting bronchodilators should depend on a patient’s perception of symptom relief.

Group C

- Single long-acting bronchodilators should be used for

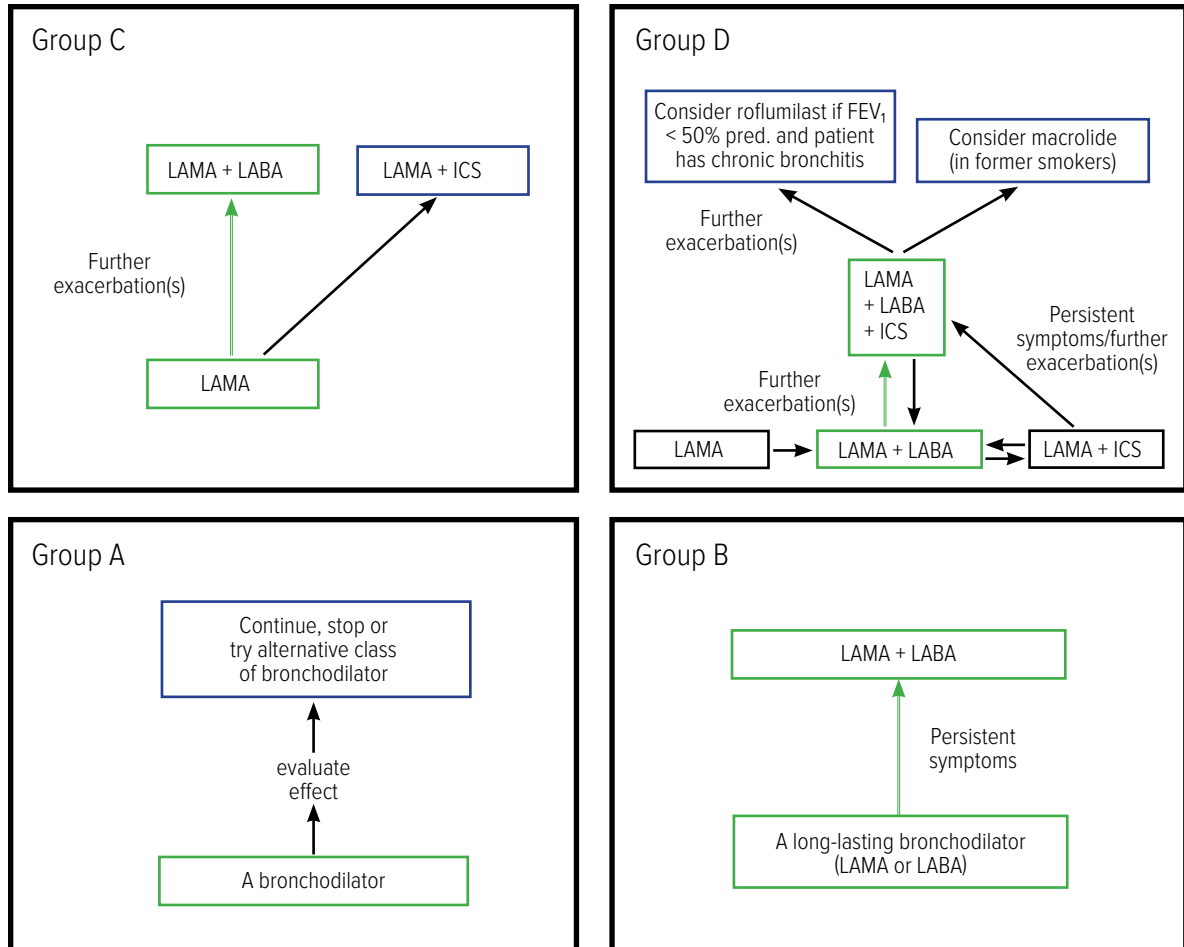
initial treatment. LAMA has shown to be superior to LABA in terms of exacerbation prevention.

- Patients with persistent exacerbations could benefit from the addition of a second long acting bronchodilator (LABA/LAMA) or using a combination of a LABA/ICS. However, ICS increases the risk for developing pneumonia in some patients, so the Gold Science Committee’s primary choice is LABA/LAMA.

Group D

- LABA/LAMA combination is recommended as a starting therapy because the combination has shown “superior” results compared to single substances. LABA/LAMA combination also performed better to a LABA/ICS combination in preventing exacerbations and other patient-reported outcomes in Group D patients. Moreover, Group D patients are at higher risk of developing pneumonia when receiving ICS.
- Patients whose initial therapy choice is LABA/ICS may have a history and/or findings suggestive of asthma-COPD overlap.
- Patients on LABA/LAMA therapy who develop further exacerbations may escalate to LABA/LAMA/ICS, though studies are still underway comparing the effects of LABA/LAMA vs. LABA/LAMA/ICS for exacerbation prevention. These patients may also switch to LABA/ICS,

FIGURE 3 Pharmacologic treatment algorithms by GOLD Grade (highlighted boxes and arrows indicate preferred treatment pathways)



Preferred treatment = →

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

though there is no evidence that switching from LABA/LAMA to LABA/ICS will lead to improved exacerbation prevention.

- If patients treated with LABA/LAMA/ICS continue to develop exacerbations, the committee recommends:
 - » Addition of roflumilast
 - » Addition of macrolide
 - » Stopping of ICS due to reported lack of efficacy, elevated risk of adverse effects, and evidence showing no significant harm from withdrawal. ●

REFERENCE

From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: <http://goldcopd.org>. Accessed 12/22/2016

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