

Considerations for the Correct Diagnosis of COPD and Its Management With Bronchodilators



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COPD is often misdiagnosed and inappropriately treated in many patients. COPD is a distinct disease from adult-onset asthma; however, some patients with COPD may present with several forms of airway disease described as asthma-COPD overlap (ACO). Bronchodilators and inhaled corticosteroids (ICS) both have a place in standard maintenance treatment of COPD and asthma; however, recommendations for use differ widely. In patients with COPD, long-acting bronchodilators are effective initial monotherapy treatment, whereas ICS monotherapy is recommended as initial treatment in patients with asthma. Clinicians need to be confident in their diagnosis to ensure that correct treatment is given because misguided treatment decisions can result in significantly increased safety risks for patients. This review highlights the differences in diagnosis and treatment between COPD, asthma, and ACO and discusses the data supporting guideline recommendations for use of bronchodilators in COPD treatment in contrast to asthma or ACO.

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Despite the availability of well-established recommendations for diagnosis and management,^{1,2} COPD is often misdiagnosed and inappropriately treated in many patients, with approximately 50% of adults with COPD in the United States misdiagnosed or undiagnosed.³ Despite a common pathophysiology,⁴ COPD is a distinct disease from adult-onset asthma and clinicians need to be confident in their diagnosis to ensure the correct treatment. To further complicate the matter, approximately 15% to 20% of patients with COPD may present with features of asthma,

described as asthma-COPD overlap (ACO).^{5,6}

Long-acting β_2 -agonist (LABA) bronchodilators and inhaled corticosteroids (ICS) both have a place in standard maintenance treatment of COPD and asthma; however, recommendations for use differ widely between diagnoses. In patients with COPD, LABAs are effective initial monotherapy treatments, whereas ICS use is only recommended in combination with LABA treatment in patients with more advanced disease.¹

ABBREVIATIONS: ACO = asthma-COPD overlap; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist

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Contrastingly, ICS monotherapy is recommended as initial treatment in patients with asthma, whereas LABA monotherapy was associated with an increase in asthma-related death, resulting in a “black box” warning being required on LABA-containing drug labels.⁷ It is recommended that LABAs always be administered in combination with ICS when treating persistent asthma of any severity.⁶

There is limited pharmacologic evidence for the optimal treatment of ACO because these patients have historically been excluded from clinical trials.^{5,8}

However, it is recommended that patients with ACO not be treated with a LABA without an ICS.⁶

Differential Diagnosis of COPD and Asthma

A diagnosis of COPD should be considered in patients who have symptoms such as dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors such as tobacco smoke or occupational exposures.¹ Importantly, postbronchodilator spirometry is required to confirm the presence of persistent airflow limitation.¹ In some patients with mild airflow obstruction, spirometry values may be normalized with smoking cessation or use of bronchodilators. In fact, up to 27.2% of subjects in a Canadian study⁹ and 15.6% of smokers in a Spanish study¹⁰ had a reversal of their COPD diagnosis. Therefore, patients initially diagnosed with COPD, even those admitted with an exacerbation, should be reassessed at follow-up to avoid overdiagnosis and overtreatment.¹¹

The diagnosis of asthma is based on the identification of a characteristic pattern of symptoms, such as wheezing, dyspnea, chest tightness, and cough, that varies over time and in intensity, accompanied by variable expiratory airflow limitation.⁶ It has been reported that a significant number of adults diagnosed with asthma and receiving treatment for the same do not actually fulfill the diagnostic criteria for asthma and they may discontinue asthma therapy.¹² Therefore, similar to the assessment of COPD, periodic reassessment of patients with asthma is crucial to avoid misdiagnosis and overtreatment.

COPD and asthma may be difficult to distinguish in clinical practice.¹³ In addition, some patients may present with characteristics of both diseases, which is described as ACO. The 2017 Global Initiative for Asthma strategy document⁶ recommends the following step-wise approach to diagnosis of ACO: recognition of

the presence of chronic airway disease, characterization of symptoms as related to asthma and COPD, and confirmation of persistent airflow limitation. The 2017 Spanish guidelines of COPD^{2,14} note that patients who meet the criterion for COPD and concomitant asthma, or a diagnosis of COPD with a very positive bronchodilator response (> 400 mL and $> 15\%$ increase in FEV₁) and/or significant blood eosinophilia (> 300 cells/mm³), can also be diagnosed as ACO.^{2,14} The main advantage of diagnosing ACO in clinical practice is to identify patients with COPD and an improved response to ICS.^{5,8} ACO has only recently been recognized as a distinct disease, and algorithms have been proposed to aid clinicians in achieving the correct diagnosis.^{2,8,14}

The diagnosis of COPD, asthma, and ACO initially requires an evaluation of exposure to respiratory risk factors, identification of the type and pattern of respiratory symptoms, and spirometry with a bronchodilator test. If required, specific tests, such as blood analysis with eosinophil counts and IgE levels, bronchoprovocation test, and sensitivity tests for pneumoallergens, can be used. A summary of the differential diagnosis and first-line therapies is depicted in Figure 1.

Treatment Options for COPD

Bronchodilators form the mainstay of maintenance treatment for COPD and are recommended as initial therapy for all Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups.¹ Patients classified as GOLD group A (low symptom burden and low exacerbation risk) are recommended to begin short- or long-acting bronchodilator treatment based on its effect on breathlessness, whereas patients classified as GOLD groups B or C (high symptom burden and low exacerbation risk, or low symptom burden and high exacerbation risk, respectively) receive a long-acting bronchodilator as initial therapy.¹

The combination of LABA and long-acting muscarinic antagonist (LAMA) bronchodilators is recommended for patients classified as GOLD groups B or C with persistent symptoms after bronchodilator monotherapy, or as initial treatment for patients classified as GOLD group D (high symptom burden and high exacerbation risk).¹ Notably, combination treatment with a LAMA/LABA increases FEV₁ and reduces symptoms and

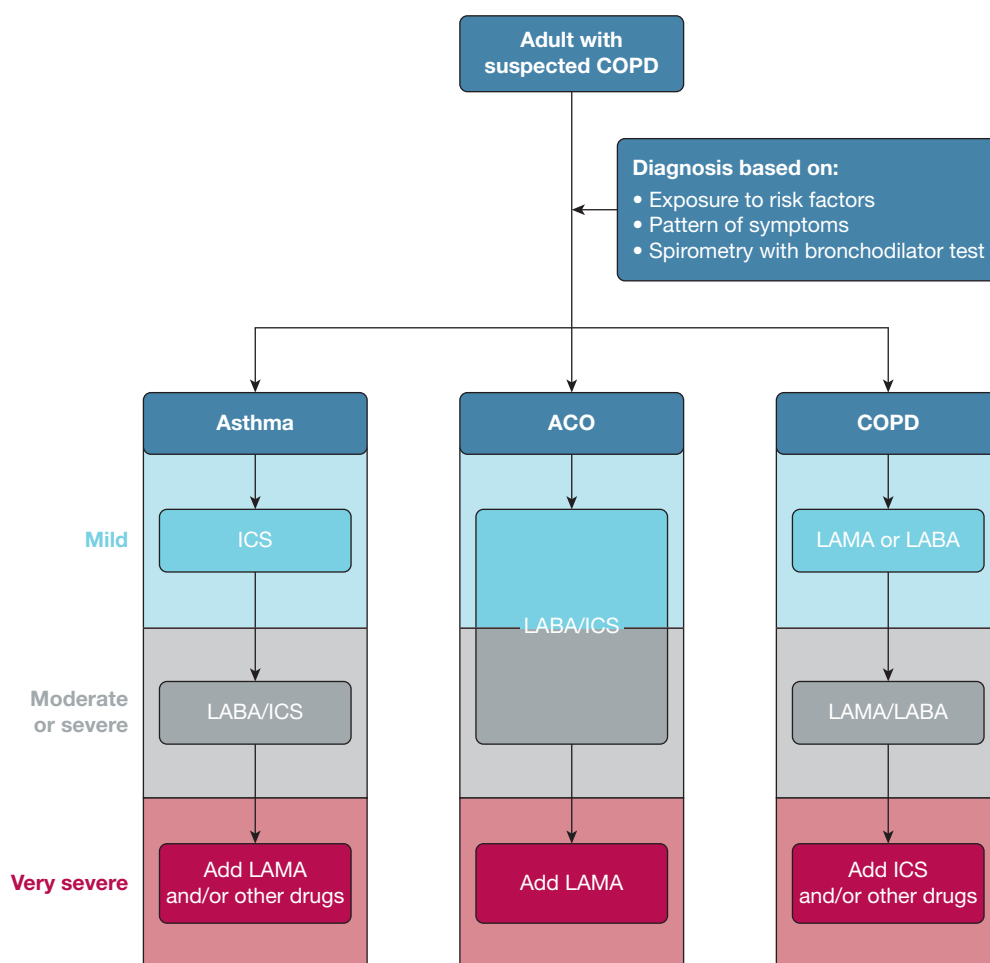


Figure 1 – Differential diagnosis and first-line therapies for COPD. ACO = asthma-COPD overlap; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist.

exacerbations compared with LAMA or LABA monotherapy.^{15,16}

Monotherapy with ICS is not recommended for the treatment of any stage of COPD.¹ This is because of an increased risk of adverse effects, such as pneumonia, with regular use.¹⁷ In patients with COPD, long-term treatment with ICS may be considered only in combination with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators.¹⁸

The costs associated with treatment are not usually taken into account in clinical practice guidelines and/or in global strategy documents such as GOLD¹; therefore, there is a need to align clinical guidelines and recommendations with the economic reality of each country. Moreover, there is a need to implement treatment regimens that provide the best cost-benefit ratio.

Efficacy of LAMA/LABA Combinations for COPD

LAMA/LABA combinations are effective treatments in patients with COPD. Combining bronchodilators of different classes, with different mechanisms and durations of action, can improve bronchodilation with a decreased risk of adverse events compared with increasing the dose of bronchodilator monotherapy.^{15,16,19} LAMA/LABA combinations directly relax airway smooth muscle through stimulation of the β_2 -adrenoceptors with a LABA and indirectly relax smooth muscle through inhibition of the neurotransmitter acetylcholine at muscarinic receptors with a LAMA.¹⁹ Treatment with a LAMA/LABA also has additive effects on airway function in patients with moderate to severe COPD, resulting in a beneficial effect on exacerbations, likely because of reduced airway resistance, improved inspiratory capacity, and reduced hyperinflation.^{20,21} In addition, LAMA/LABA

combinations offer significant improvements in lung function parameters compared with their component monotherapies^{15,22} and compared with LABA/ICS.²³⁻²⁶ Treatment with a LAMA/LABA generally improves symptoms such as breathlessness, quality of life, and health status vs monotherapies.^{15,27-30} Some LAMA/LABA combinations have also demonstrated improvements in nighttime and early morning symptoms vs monotherapies, which are known to be impactful at the individual patient level (eg, decreased sleep disturbances).²³

Choice of LAMA/LABA should be individualized for each patient's preferences and degree of disease burden because no recommendations currently prioritize any specific LAMA/LABA therapy over another, and no LAMA/LABA therapy is approved for specific subgroups of patients with COPD.^{23,27,29} Choice of device must also be carefully considered on an individual basis because each device has advantages and limitations that ultimately affect patient response to treatment and use of health-care resources.^{31,32} A summary of the efficacy of a fixed LABA/LAMA combination compared with long-acting bronchodilator monotherapy and LABA/ICS is described in Table 1.

Safety of LAMA/LABA Combinations for COPD

The safety profile of LAMA/LABA combinations in patients with COPD is well documented, with no safety concerns vs monotherapies or LABA/ICS.^{15,28-30,33-35} A recent meta-analysis of LABA/LAMA combinations indacaterol/glycopyrronium, umeclidinium/vilanterol, aclidinium/formoterol, and tiotropium/olodaterol demonstrated no difference in adverse events compared with the respective LABA alone and fewer adverse events compared with LABA/ICS.²⁹

Efficacy of ICS in Asthma and ACO

Despite the recommendation for limited use in patients with COPD, ICS therapy is an encouraged treatment

option for patients with asthma. ICS as initial monotherapy or in combination with LABAs effectively control the symptoms of asthma.³⁶ ICS alone has been shown to offer benefits such as improved lung function and symptom control and decreased airway hyperresponsiveness compared with placebo.⁶ ICS/LABA in combination has demonstrated improvements in symptoms, lung function, and asthma control compared with monocomponents and placebo³⁷ and is recommended in adult patients with asthma with inadequate symptom control on ICS monotherapy.⁶ It has also been suggested that LABA/ICS may be modestly more effective at improving lung function than an increased dose of ICS monotherapy in patients with asthma.³⁷

The clinical and inflammatory characteristics of patients with ACO support the use of anti-inflammatory treatment (ie, an ICS/LABA combination) as initial therapy because of the beneficial effect of ICS in asthma.³⁸ ACO has been associated with a higher degree of bronchial eosinophilic inflammation than COPD alone; therefore, ICS treatment offers a greater clinical and spirometric response and justifies its use in these patients.¹ Treatment with ICS/LABA has also demonstrated improvements in a composite end point of hospitalization or death in patients with COPD and a codiagnosis of asthma compared with patients with COPD alone.³⁹

Safety Issues With ICS in COPD

Although there is a minor clinical role for ICS in COPD management, it is important to note that patients with COPD are at risk of ICS-related side effects. Increased risk of pneumonia is the most troublesome adverse effect of ICS in patients with COPD given the size of the relative increase in risk, the frequency, and the associated increase in mortality.¹⁷ The long-term use of ICS in COPD is associated with changes in the lung microbiome, resulting in changes in the bacterial load and species in the airways, particularly for the more frequently occurring pathogenic bacteria such as

TABLE 1] Comparative Efficacy of LABA/LAMA vs Long-Acting Bronchodilator Monotherapy and LABA/ICS for the Treatment of COPD

Therapy	FEV ₁	Dyspnea	HRQoL	Exacerbations	Exercise Capacity
LABA/LAMA vs monotherapies	+++	++	++	+	+
LABA/LAMA vs LABA/ICS	++	++	+	++	NA

This table is based on the authors' interpretation of data from the references.^{15,22,24-30,33-35} + = mild improvement; ++ = moderate improvement; +++ = high improvement; HRQoL = health-related quality of life; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; NA= not assessed.

Haemophilus influenzae, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.⁴⁰ In addition, patients with COPD are likely to be older and typically have several comorbidities that may make them more susceptible to adverse effects of ICS treatment, such as skin thinning and bruising.⁴¹ Other safety concerns include increased risk of bone fractures, an increase in blood glucose, an increase in glycosylated hemoglobin, and risk of insulin dependence among patients with diabetes, concerns of adrenal insufficiency, and an excess of cataracts.^{17,41}

The frequent long-term and unjustified use of ICS in patients with COPD makes safety issues of particular concern. Intensive use of ICS, alone or in combination with LABA, has been observed in patients without an indication for ICS use (ie, COPD of mild severity), resulting in an unwarranted risk of serious side effects derived from long-term use.⁴² In a large study of 11,858 patients with COPD from a longitudinal primary care database, approximately 25% of patients classified as GOLD groups A, B, and C were prescribed LAMA/LABA/ICS triple therapy within 1 year after diagnosis, despite a lack of indication for use, and a small proportion even received triple therapy prior to diagnosis.⁴³ This inappropriate use of ICS exposes patients to serious side effects early in disease progression and wastes health-care resources.⁴¹ A lack of understanding of the real impact of the side effects of ICS on the COPD population in the clinical setting is evidenced by a recent panel of COPD experts who were unable to achieve agreement regarding questions on the side effects of long-term use of ICS, with answers differing widely among the panel.⁴² Many patients with COPD do not need ICS, and clinical trials and real-world evidence show that patients can be safely withdrawn from ICS therapy, suggesting that the most appropriate role of ICS in COPD management has yet to be determined.^{44,45}

Phenotypes of Patients With COPD Who Respond to ICS

Despite many patients with COPD receiving ICS earlier than indicated,⁴⁶ recommendations specify that ICS should be used only in patients with more severe COPD (GOLD group D) who develop additional exacerbations after optimal LAMA/LABA therapy.^{1,2,18} Given that some patients do not respond to ICS and that ICS therapy is associated with an increased risk of side effects, it is advantageous to identify patients who are likely to respond favorably to ICS therapy.

Eosinophil counts have been proposed as the most promising biomarker of ICS response because patients with COPD with asthmatic features tend to have higher eosinophil counts than those without.⁸ Patients with COPD with the ACO feature of elevated peripheral eosinophils have shown to be significantly more likely to have a significant therapeutic response to ICS/LABA than patients with COPD alone, in particular in terms of a reduction in the risk of exacerbations.⁴⁷ Meanwhile, minimal efficacy of ICS/LABA in patients with low levels of blood eosinophils, together with the risk of side effects, advises against their indication in this context.^{8,47} There is currently little agreement on an appropriate cutoff value for eosinophils indicating ICS response in COPD, with recommendations between 2% and 5% of total cell count, and a suggested absolute cell count between 200 and 300 cells/ μ L, indicating that further evidence is needed to identify an optimal cutoff level to predict response.⁸

Eosinophil levels have also been suggested as a biomarker to predict response to ICS withdrawal.⁴⁵ A post hoc analysis of patients with severe to very severe COPD and a history of exacerbations proposed that eosinophil counts of $\geq 4\%$ or ≥ 300 cells/ μ L may identify a deleterious effect of ICS withdrawal, an effect not seen in most patients with eosinophil counts below these thresholds.⁴⁸ Patients with high eosinophil counts (≥ 400 cells/ μ L) were also more likely to experience increased exacerbation rates after ICS withdrawal if they had experienced two or more exacerbations in the last year,⁴⁹ suggesting that both eosinophil levels and exacerbation history may be a more effective marker of response to ICS withdrawal than eosinophil levels alone.⁴⁵

Other biomarkers have been suggested to predict the presence of ACO phenotype in patients with COPD as an indicator of ICS response, including serum IgE levels, fractional exhaled nitric oxide, and CT scan parameters. However, challenges such as poor standardization of measurements and lack of clinically defined relevant thresholds have resulted in limited clinical application thus far.⁸ There is a need for better predictive biomarkers in patients with COPD to establish optimal diagnosis and treatment options.

Summary

Overall, clinicians need to be confident in their ability to accurately diagnose COPD and distinguish symptoms from those of asthma and ACO. Accurate

diagnosis is vital to ensure that patients receive the most appropriate treatment. Evidence has shown that LAMA/LABA combinations are an effective and safe therapeutic option in patients with COPD and play an important role in reducing the risk of exacerbations in patients for whom they are indicated. Bronchodilators are recommended as initial therapy for all GOLD groups, with the GOLD 2017 strategy document¹ recommending a LAMA/LABA combination for patients classified as GOLD groups B or C with persistent symptoms after bronchodilator monotherapy, or as initial treatment for patients classified as GOLD group D (high symptom burden and high exacerbation risk). Clinicians should only consider adding ICS in those patients who experience persistent exacerbations despite optimal treatment with LAMA/LABA.^{1,50} In addition to careful symptom assessment, the use of eosinophil counts may play an advantageous role in predicting those patients who are most likely to benefit from the addition of ICS therapy in COPD.

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