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# COPD inhaler therapy: A path to success

Keys to therapeutic success include choosing the right device and drug regimen, providing rigorous patient education, and reducing environmental exposures.

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## PRACTICE RECOMMENDATIONS

› *Follow guideline advice that (1) in general, short-acting beta-agonists (SABAs) are not for daily use in stable chronic obstructive pulmonary disease (COPD) but (2) agents in this class of drugs might have a role in relieving occasional COPD-associated dyspnea.* (C)

› *Prescribe albuterol over levalbuterol when a SABA is indicated because of the lower cost of albuterol, its comparative efficacy, and its lower incidence of tachycardia and palpitations, even in patients with cardiovascular disease.* (B)

› *Avoid the use of an inhaled corticosteroid, or consider withdrawing inhaled corticosteroid therapy, in patients with COPD whose blood eosinophil count is < 100 cells/μL or who have repeated bouts of pneumonia or a history of mycobacterial infection.* (B)

**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

Managing chronic obstructive pulmonary disease (COPD) presents a significant challenge to busy clinicians in many ways, especially when one is approaching the long list of inhaled pharmaceutical agents with an eye toward a cost-effective, patient-centered regimen. Inhaled agents remain expensive, with few available in generic form.

Our primary goal in this article is to detail these agents' utility, limitations, and relative cost. Specifically, we review why the following considerations are important:

- Choose the right delivery device and drug while considering patient factors.
- Provide patient education through allied health professionals.
- Reduce environmental exposures.
- Rethink the use of inhaled corticosteroids (ICS).
- Understand the role of dual therapy and triple therapy.

There are numerous other treatment modalities for COPD that are recommended in national and international practice guidelines, including vaccination, pulmonary rehabilitation, home visits, phosphodiesterase-4 inhibitors, oral glucocorticoids, supplemental oxygen, and ventilatory support.[1] Discussion of those modalities is beyond the scope of this review.

## Pathophysiology and pharmacotherapy targets

COPD is characterized by persistent respiratory symptoms and airflow limitation, usually due to airway or alveolar abnormalities, or both, caused by environmental and host factors.[2] Sustained lung parenchymal irritation results from exposure to noxious fumes generated by tobacco, pollution, chemicals, and cleaning agents. Host factors include lung immaturity at birth; genetic mutations, such as alpha-1 antitrypsin deficiency and dysregulation of elastase; and increased reactivity of bronchial smooth muscles, similar to what is seen in asthma.[1]

Guidelines recommend reassessing inhaler technique at every visit and when evaluating treatment response.

Improving ventilation with the intention of relieving dyspnea is the goal of inhaler pharmacotherapy; targets include muscarinic receptors and beta 2-adrenergic receptors that act on bronchial smooth muscle and the autonomic nervous system. Immune modulators, such as corticosteroids, help reduce inflammation around airways.[1] Recent pharmacotherapeutic developments include combinations of inhaled medications and expanding options for devices that deliver drugs.

## Delivery devices: Options and optimizing their use

Three principal types of inhaler devices are available: pressurized metered-dose inhalers (MDIs), dry-powder inhalers (DPIs), and soft-mist inhalers (SMIs). These devices, and nebulizers, facilitate medication delivery into the lungs (**TABLE 1**[3-9]).

**Errors in using inhalers affect outcome.** Correct inhaler technique is essential for optimal delivery of inhaled medications. Errors in technique when using an inhaled delivery device lead to inadequate drug delivery and are associated with poor outcomes: 90% of patients make errors that are classified as critical (ie, those that reduce drug delivery) or noncritical.[2] Critical inhaler errors increase the risk of hospitalization and emergency department visits, and can necessitate a course of oral corticosteroids.[10] Many critical errors are device specific; several such errors are described in **TABLE 1**.[3-9]

**Patient education** is necessary to ensure that drug is delivered to the patient consistently, with the same expectation of effect seen in efficacy studies (which usually provide rigorous inhaler technique training and require demonstration of proficiency).[1,2,10] For the busy clinician, a multidisciplinary approach, discussed shortly, can help. Guidelines developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend that inhaler technique be reassessed at every visit and when evaluating treatment response.[1] **TABLE 1**[3-9] provides information on each device type, patient requirements for use, proper technique, common errors in use, and tips for optimizing delivery.

Inhaler education and assessment of technique that is provided to patients in collaboration with a clinical pharmacist, nursing staff, and a respiratory therapist can help alleviate the pressure on a time-constrained

IMAGE © JOE GORMAN

**TABLE 1**

## Considerations in choosing an inhaler device for COPD treatment[3-9]

| Device | Delivery mechanism[3] | Patient coordination and requirements for delivery | Optimal peak inspiratory flow rate[3a] | Delivery technique | Common patient technique errors that affect drug delivery[4-7] (% of patients observed committing the error) | Tips to optimize delivery |
|---|---|---|---|---|---|---|
| Metered-dose inhaler | Pressurized canister of active drug suspended in a mixture of propellants, surfactants, and dispersal agents | High-velocity delivery requires hand–breath coordination or use of a spacer or holding chamber | ~30 L/min | Slow, deep inhalation coordinated with actuation, followed by a 10-second breath hold | Not exhaling before actuation (50%)<br>Forceful inhalation after actuation (52%)<br>Absence or too short of a breath hold after dose administration (53%)<br>Actuation in second half of inhalation (18%) | Use with spacer<br>Shake well before each use<br>Inhale immediately after actuation into spacer |
| Dry-powder inhaler | Breath-actuated device that delivers active dry drug from punctured capsule or reservoir | Fewer concerns about synchrony because the device is breath actuated | 30-60 L/min | Fast, deep inhalation after loading dose | Inadequate force and depth of inhalation (24%-28%)<br>Stopping inhalation too soon (26%-29%)<br>Exhaling into the mouthpiece after loading drug (19%-22%) | Exhale fully away from mouthpiece<br>Provide education about inhaler position if necessary (ie, the discus must remain horizontal after loading the drug) |
| Soft-mist inhaler | Spring system that delivers measured volume of drug solution as high fine-particle fraction by low velocity (over approximately 1.2 sec) | Requires less patient coordination than a pressurized metered-dose inhaler, due to slower delivery | 20-60 L/min[9] | Slow, deep breath coordinated with medication actuation | Not exhaling prior to dose delivery (48%)<br>Absent or inadequate breath hold after delivery (31%)<br>Not taking a slow, deep breath while pressing dose-actuation button (28%) | Follow the mnemonic "TOP": *T*wist canister, *O*pen lid, *P*ush button<br>Mouth must be on mouthpiece before pushing the button |
| Nebulizer | Aerosolization of drug particles from liquid solution by air or oxygen | Requires the least patient participation and timing for medication delivery of any delivery device | N/A | Deep breaths through mouth until all medication is nebulized | N/A | Ensure all medication has been nebulized |

N/A, not applicable.

[a] The peak inspiratory flow rate affects the location of drug deposition and disaggregation and aerosolization of dry powders; it is therefore a consideration when selecting a delivery device for a given patient.[8,9]

primary care physician. Furthermore, pharmacist involvement in the COPD management team meaningfully improves inhaler technique and medication adherence.[6,7] Intervention by a pharmacist correlates with a significant reduction in number of exacerbations; an increased likelihood that the patient has a COPD care plan and has received the pneumococcal vaccine; and an improvement in the mean health-related quality of life.[11,12]

In primary care practices that lack robust multidisciplinary resources, we recommend

utilizing virtual resources, such as educational videos, to allow face-to-face or virtual education. A free source of such resources is the COPD Foundation,[a] a not-for-profit organization funded partly by industry.

## Short- and long-acting inhaled medications for COPD

Each class of inhaled medication for treating COPD is discussed broadly in the following sections. **TABLE 2**[1] provides details about individual drugs, devices available to deliver them, and starting dosages.

### Short-acting agents

These drugs are available in MDI, SMI, and nebulizer delivery devices. When portability and equipment burden are important to the patient, we recommend an MDI over a nebulizer; an MDI is as efficacious as a nebulizer in improving forced expiratory volume in 1 second ($FEV_1$) and reducing the length of hospital stay for exacerbations.[4]

**Short-acting beta 2-adrenergic agonists (or beta-agonists [SABAs]).** Beta-agonists are typically used to treat exacerbations. They facilitate bronchodilation by upregulating cyclic adenosine monophosphate, preventing smooth-muscle contraction, and reducing dynamic hyperinflation. The effect of a SABA lasts 4 to 6 hours.

In general, SABAs are not recommended for daily use in stable COPD. However, they can be useful, and appropriate, for treating occasional dyspnea and can confer additional symptom improvement when used occasionally along with a long-acting beta 2-adrenergic agonist (or beta-agonist [LABA]; discussed later).[1]

Albuterol, a commonly used SABA, is less expensive than, and just as effective as, same-class levalbuterol for decreasing breathlessness associated with acute exacerbations. There is no significant difference between the 2 drugs in regard to the incidence of tachycardia or palpitations in patients with cardiovascular disease.[13]

Although no significant differences have been observed in outcomes when a nebulizer or an MDI is used to administer a SABA, it's wise to avoid continuous SABA nebulizer therapy, due to the increased risk of disease transmission through the generation of droplets.[1,4] Instead, it's appropriate to use an MDI regimen of 1 to 3 puffs every hour for 2 to 3 hours, followed by 1 to 3 puffs every 2 to 4 hours thereafter, based on the patient's response.[1,4]

**Short-acting muscarinic antagonists (SAMAs).** Muscarinic antagonists achieve bronchodilation by blocking acetylcholine on muscarinic receptors. We do not specifically recommend SAMAs over SABAs for treating COPD exacerbations in our patients: There is no difference in improvement in $FEV_1$ during an acute exacerbation. Nebulized delivery of a SAMA raises concern for an increase in the risk of acute narrow-angle glaucoma, a risk that can be reduced by using a mask during administration.[1,14]

**SABA + SAMA.** One combination formulation of the 2 short-term classes of drugs (albuterol [SABA] + ipratropium [SAMA]), US Food and Drug Administration (FDA)–approved for every-6-hour dosing, is available for SMI delivery devices and nebulizers. In the setting of a hospitalized patient who requires more frequent bronchodilator dosing, we use albuterol and ipratropium delivered separately (ie, dosed independently), with ipratropium dosed no more frequently than every 4 hours.

### Long-acting agents

The mechanisms of long-acting agents are similar to those of their short-acting counterparts. The recommendation is to continue use of a long-acting bronchodilator during exacerbations, when feasible.[1]

**LABA monotherapy** reduces exacerbations that result in hospitalization (number needed to treat [NNT] = 39, to prevent 1 hospitalization in an 8-month period).[15] Specifically, formoterol at higher dosages reduces exacerbations requiring hospitalization (NNT = 23, to prevent 1 exacerbation in a 6-month to 3-year period).[15] Evidence supports better control of symptoms when a LABA is combined with a long-acting muscarinic antagonist (LAMA; discussed shortly).[1,15]

Adverse effects of LABAs include sinus tachycardia, tachyphylaxis, somatic trem-

**Continue use of a long-acting bronchodilator during exacerbations, when feasible.**

[a] www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Educational-Video-Series.aspx

**TABLE 2**

## Inhaled pharmacotherapeutic agents for COPD[1]

| Drug | Device | Usual starting dosage | Notable adverse effects | Cost[a] | Considerations |
|---|---|---|---|---|---|
| **SABA** | | | | | |
| Albuterol | MDI, nebulizer | MDI: 2 inhalations (180 mcg) q4h<br>Nebulizer: 1 vial (2.5 mg) q4h | *Class adverse effects*:<br>• Tachycardia, tremor<br>• Cardiac arrhythmia (in susceptible patients) | MDI: $18/8.5-g inhaler[b]<br>Nebulizer: $10/25 2.5-mg + 3-mL vials[b] | Rapid onset<br>Relatively short duration of action |
| Levalbuterol | MDI, nebulizer | MDI: 2 inhalations (90 mcg) q4h<br>Nebulizer: 1 vial (1.25 mg) q4h | | MDI: $32/200-actuation inhaler[b]<br>Nebulizer: $34/24 1.25-mg/3-mL vials[b] | Generally reserved for patients who experience adverse effects related to albuterol (eg, tachycardia) |
| **LABA** | | | | | |
| Arformoterol | Nebulizer | 1 vial (15 mcg) bid | *Class adverse effects*:<br>• Tachycardia, tremor<br>• Cardiac arrhythmia (in susceptible patients) | $303 | |
| Formoterol | Nebulizer | 1 vial (20 mcg) bid | | $301 | |
| Indacaterol | DPI | 1 capsule (75 mcg) qd | | $259 | Possible cough after inhalation |
| Olodaterol | SMI | 2 inhalations (5 mcg) qd | | $226 | |
| Salmeterol | DPI | 1 inhalation (50 mcg) bid | | $408 | |
| **SAMA** | | | | | |
| Ipratropium bromide | MDI, nebulizer | MDI: 2 inhalations (34 mcg) q6h<br>Nebulizer: 0.5 mg (1 vial) q6h | Possible increase in ocular pressure, urinary retention, and dry mouth | MDI: $438/12.9-g inhaler<br>Nebulizer: $12/25 0.5-mg (0.02%) vials[b] | Use with caution in patients with narrow-angle glaucoma (risk of an increase in intraocular pressure) |
| **LAMA** | | | | | |
| Aclidinium bromide | DPI | 1 inhalation (400 mcg) bid | *Class adverse effects*:<br>Possible increase in ocular pressure, urinary retention, and dry mouth | $374 | |
| Glycopyrrolate | DPI, nebulizer | DPI: 1 capsule (15.6 mcg) bid<br>Nebulizer: 1 vial (25 mcg) bid | | DPI: $391<br>Nebulizer: $1163 | |
| Revefenacin | Nebulizer | 1 neb (175 mcg) qd | | $1135 | |
| Tiotropium | DPI, SMI | Handihaler: 1 capsule (18 mcg) qd<br>Respimet: 2 inhalations (5 mcg) qd | | Handihaler: $472<br>Respimet: $472 | |
| Umeclidinium | DPI | 1 inhalation (62.5 mcg) qd | | $352 | |

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ors, and, less commonly, hypokalemia—the latter specific to the LABA dosage and concomitant use of a thiazide diuretic. Other adverse effects include a mild decrease in the partial pressure of $O_2$ and, in patients with heart failure, increased oxygen consumption. Although higher dosages are *not* associated with an increased incidence of nonfatal adverse events, there appears to be no additional benefit to higher dosages in regard to mortality, particularly in patients with stable COPD.[1,15]

**TABLE 2**

## Inhaled pharmacotherapeutic agents for COPD[1] (*cont'd*)

| Drug | Device | Usual starting dosage | Notable adverse effects | Cost[a] | Considerations |
|---|---|---|---|---|---|
| **SABA + SAMA** | | | | | |
| Albuterol + ipratropium | SMI, nebulizer | SMI: 1 inhalation q6h<br>Nebulizer: 1 neb (3 mg + 0.5 mg) q6h | See individual class adverse effects | SMI: $439<br>Nebulizer: $13/30 3-mL (3 mg/0.5 mg) vials[b] | SABA + SAMA combination achieves greater bronchodilation than monotherapy |
| **LAMA + LABA** | | | | | |
| Aclidinium + formoterol | DPI | 1 inhalation (400 mcg + 12 mcg) bid | See individual class adverse effects | $975 | |
| Glycopyrrolate + formoterol | MDI | 2 inhalations (18 mcg + 9.6 mcg) bid | | $392 | |
| Glycopyrronium bromide + indacaterol | DPI | 1 capsule (15.6 mcg + 27.5 mcg) bid | | $365 | |
| Tiotropium + olodaterol | SMI | 2 inhalations (5 mcg + 5 mcg) qd | | $424 | |
| Umeclidinium + vilanterol | DPI | 1 inhalation (62.5 mcg + 25 mcg) qd | | $430 | |
| **LABA + ICS** | | | | | |
| Formoterol + budesonide | MDI | 2 inhalations (320 mcg + 9 mcg) bid | LABA: See class adverse effects<br>ICS: Thrush, hoarseness and throat irritation, arthralgias | $203 | |
| Formoterol + mometasone | MDI | 2 inhalations (200 mcg + 10 mcg) bid | | $311 | |
| Salmeterol + fluticasone propionate | DPI, MDI | DPI: 1 inhalation (250 mcg + 50 mcg) bid<br>MDI: 2 inhalations (230 mcg + 42 mcg) bid | | DPI: $96<br>MDI: —[c] | |
| Vilanterol + fluticasone furoate | DPI | 1 inhalation (100 mcg + 25 mcg) qd | | $370 | |
| **LABA + LAMA + ICS** | | | | | |
| Budesonide + glycopyrrolate + formoterol | MDI | 2 inhalations (320 mcg + 18 mcg + 9.6 mcg) bid | See individual class adverse effects | $540 | |
| Fluticasone + umeclidinium + vilanterol | DPI | 1 inhalation (100 mcg + 62.5 mcg + 25 mcg) qd | | $593 | |

Costs are for 30-day supply, unless otherwise specified. Prices without footnote "b" are available as brand-name product only.

DPI, dry-powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist; SMI, soft-mist inhaler.

[a] Source: GoodRx (www.goodrx.com).

[b] Cost of generic drug.

[c] Hydrofluoroalkane (HFA)-propelled formulation of salmeterol + fluticasone propionate (Advair HFA) is not listed on GoodRx.com.

**LAMA.** Monotherapy with a LAMA reduces the severity of COPD symptoms and reduces the risk of exacerbations and hospitalization (NNT = 58, to prevent 1 hospitalization in a 3 to 48–month period).[16] Tiotropium is superior to LABA as monotherapy in (1) reducing exacerbations (NNT = 33, to prevent 1 exacerbation in a 3 to 12–month period) and (2) being associated with a lower rate of all adverse events.[17] LAMAs also confer addi-

tional benefit when used in combination with agents of other classes, which we discuss in a bit.

The most commonly reported adverse effect of a LAMA is dry mouth. Some patients report developing a bitter metallic taste in the mouth.[1]

**ICSs** are not recommended as monotherapy in COPD.[1] However, an ICS can be combined with a LABA to reduce the risk of exacerbations in patients with severe COPD (NNT = 22, to prevent 1 exacerbation per year).[18] However, this combination increases the risk of pneumonia in this population (number needed to harm [NNH] = 36, to cause 1 case of nonfatal pneumonia per year).[18]

ICSs increase the incidence of oropharyngeal candidiasis and hoarseness. In addition, ICSs increase the risk of pneumonia in some patients with COPD[18]—in particular, current smokers, patients ≥ 55 years of age, and patients with a history of pneumonia or exacerbations, a body mass index < 25, or severe COPD symptoms.[1,18] ICS therapy does reduce the risk of COPD exacerbations in patients with a history of asthma or with eosinophilia > 300 cells/μL and in those who have a history of hospitalization for COPD exacerbations.[19,20]

The risk of pneumonia is not equal across all ICS agents. Fluticasone increases the risk of pneumonia (NNH = 23, to cause 1 case of pneumonia in a 22-month period).[21] Budesonide showed no statistically significant increase in risk of pneumonia.[22] However, further studies on the risk of pneumonia with budesonide are needed because those cited in the Cochrane review[21] were much smaller trials, compared to trials of fluticasone, and of low-to-moderate quality. Furthermore, evidence is mixed whether ICS monotherapy in COPD worsens mortality during an 18-month study period.[21-23]

For these reasons, it's reasonable to (1) exercise caution when considering the addition of an ICS to LABA therapy and (2) limit such a combination to the setting of severe disease (as discussed already).

**LABA + LAMA.** In a trial of patients with moderate-to-severe COPD, combining a LABA and a LAMA did not reduce the risk of exacerbations or hospitalizations, compared to LABA or LAMA monotherapy, but did improve subjects' reported daily symptoms and quality of life scores (using the St. George's Respiratory Questionnaire[b]; NNT = 14 [LAMA monotherapy] and NNT = 9 [LABA monotherapy], both in a 3 to 12–month period).[24] However, another study that looked at patients with moderate-to-severe COPD found that combining a LABA and a LAMA led to fewer exacerbations (NNT = 22, to prevent 1 exacerbation in a 3 to 12–month period) and a lower risk of pneumonia (NNT = 93, to prevent 1 case of pneumonia in a 3 to 12–month period) than LABA + ICS.[25]

**LABA + ICS.** This dual therapy is falling out of favor, compared to treatment with LABA + LAMA, because LABA + ICS formulations are less effective at reducing exacerbations and increase the risk of pneumonia in patients with moderate-to-severe COPD.[1,25] However, LABA + ICS therapy still has a role in a subset of patients with COPD (discussed in the section on ICS). A LABA combined with an ICS does reduce exacerbations in patients with severe COPD (NNT = 22, to prevent 1 exacerbation per year).[18] Expect that the reported rates of candidiasis, hoarseness, and pneumonia associated with an ICS will be similar with LABA + ICS.[18]

**LABA + LAMA + ICS.** These are the newest combination inhaled agents approved for clinical use. It is recommended that escalation to such triple therapy be reserved for patients with persistent dyspnea on LAMA + LABA therapy and who have the factors (previously described) that suggest benefit from adding an ICS.[1] Several clinical trials have provided guidance:

- In the 2018 TRIBUTE trial,[26] beclometasone (ICS) + formoterol (LABA) + glycopyrronium (LAMA)[c] outperformed indacaterol (LABA) + glycopyrronium for preventing moderate-to-severe exacerbations (NNT = 11, to prevent 1 exacerbation per year) in patients with symptomatic

**When portability and equipment burden are important to the patient, consider a metered-dose inhaler (MDI) over a nebulizer: An MDI is equally efficacious.**

[b] www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php

[c] Not an FDA-approved combination inhaled-agent treatment; approved in the European Union, under various brand names, by the European Medicines Agency.

COPD who have severe or very severe airflow resistance and a history of a moderate-to-severe exacerbation during the previous year.

- In the 2017 TRINITY trial,[27] beclometasone + formoterol + glycopyrronium[c] outperformed tiotropium (LAMA) in preventing moderate-to-severe exacerbations (NNT = 9, to prevent 1 exacerbation per year) in patients with an $FEV_1$ < 50% and a history of ≥ 1 moderate-to-severe exacerbation during the previous year.
- In the 2020 ETHOS trial,[28] budesonide + formoterol + glycopyrronium (approved by the FDA in 2020 under the brand name Breztri) outperformed both glycopyrrolate + formoterol (LABA) and budesonide (ICS) + formoterol in preventing moderate-to-severe exacerbations (NNT = 56 and 34, respectively, to prevent 1 exacerbation per year) in patients with moderate-to-severe COPD who had a history of ≥ 1 exacerbation in the previous year. Additionally, higher-dose budesonide + formoterol + glycopyrronium reduced 1-year mortality to a modest degree compared to glycopyrrolate + formoterol (NNT = 100, to prevent 1 death in a 12-month period).
- A 2016 Cochrane review that compared tiotropium + LABA + ICS to tiotropium monotherapy[29] showed improvement in $FEV_1$ and patient-reported symptoms and quality of life scores. However, the review showed no difference in exacerbations or hospitalizations over a 1-year period.

### Mitigating environmental exposures that affect inhaler medication efficacy

**Tobacco smoke.** Emphasizing smoking cessation is highly relevant in patients who are still smoking. Smoking impedes the efficacy of ICSs in reducing exacerbations of COPD.[30] Along with improved lung function, former smokers with COPD experience fewer exacerbations (NNT = 73, to prevent 1 exacerbation in a 4-year period for all former smokers; NNT = 33, to do so for smokers who quit > 10 years ago).[31,32]

A 2005 Veterans Health Administration study showed reduced mortality in smokers who were enrolled in a 10-week smoking cessation program, had access to nicotine replacement therapy, and received strong physician messaging.[33] Despite a 20% to 25% quit rate, the NNT was 56 to prevent 1 death in 14.5 years across the entire group. It is worth having patients take advantage of this 3-pronged approach if it is available in your community or health system.

**Exposure to air pollution.** Air pollutants other than tobacco smoke remain important modifiable factors that impact COPD. These include organic and inorganic dusts, chemical agents and fumes, and burning of solid biomass (eg, wood, coal) indoors in open fires or poorly functioning stoves.[1] With this risk in mind, counsel patients regarding efficient home ventilation, use of nonpolluting cooking stoves, and the reduction of occupational exposure to these potential irritants.

## GOLD approach to starting and adjusting inhaled therapy

### Initiating inhaled therapy

A good resource for family physicians is the GOLD refined ABCD assessment scheme for initiating inhaler therapy that integrates symptoms and exacerbations (**TABLE 3**[1]). To assess the severity of dyspnea, either the Modified Medical Research Council (mMRC) Questionnaire or COPD Assessment Test (CAT) can be used. A moderate exacerbation requires an oral corticosteroid or antibiotic, or both; a severe exacerbation requires an emergency department visit or hospitalization, or both. **TABLE 3**[1] offers a guide to choosing initial therapy based on these factors.[1]

### Following up on and adjusting an inhaler regimen

Adjust inhaler pharmacotherapy based on whether exacerbations or daily symptoms of dyspnea are more bothersome to the patient.

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**The continuous use of short-acting beta-agonist nebulizer therapy can increase the risk of disease transmission through the generation of droplets.**

[c] Not an FDA-approved combination inhaled-agent treatment; approved in the European Union, under various brand names, by the European Medicines Agency.

**TABLE 3**

## The Global Initiative for Chronic Obstructive Lung Disease (GOLD) refined ABCD approach to COPD management[1]

| | Initial pharmacological treatment | |
|---|---|---|
| ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization | **Group C**<br>LAMA | **Group D**<br>LAMA *or*<br>LAMA + LABA[a]<br>*or* ICS + LABA[b] |
| 0 or 1 moderate exacerbations (not leading to hospital admission) | **Group A**<br>A bronchodilator | **Group B**<br>A long-acting bronchodilator (LABA *or* LAMA) |
| | mMRC 0-1, CAT < 10 | mMRC ≥ 2, CAT ≥ 10 |

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council (score).

[a] Consider if highly symptomatic (eg, CAT > 20).

[b] Consider if eosinophil count ≥ 300 cells/μL.

Source: © 2021, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL, USA.

Escalation of therapy involves adding other long-acting agents and is warranted for patients with exacerbations or severe or worsening dyspnea. Before escalating therapy with additional agents, reassess the appropriateness of the delivery device that the patient has been using and assess their adherence to the prescribed regimen.[1]

**Dyspnea predominates.** Escalate with LABA + LAMA. For a patient already taking an ICS, consider removing that ICS if the original indication was inappropriate, no response to treatment has been noted, or pneumonia develops.[1]

**Exacerbations predominate.** Escalate with LABA + LAMA or with LABA + ICS. Consider adding an ICS in patients who have a history of asthma, eosinophilia > 300 cells/uL, or eosinophilia > 100 cells/uL and 2 moderate exacerbations or 1 severe (ie, hospitalizing) exacerbation. This addition of an ICS results in dual or triple therapy (ie, either LABA + ICS or LABA + LAMA + ICS).[1]

**Unclear what predominates?** Follow the exacerbation predominance pathway.[1]

Additional decision-making might be necessary in several circumstances:

- For the patient who requires further titration beyond these pathways, consider triple therapy as LABA + LAMA + ICS, unless the eosinophil count is < 100 cell/μL.[1]
- Consider de-escalating ICS therapy if the patient develops pneumonia, there is a lack of demonstrated benefit, or the initial indication was uncertain or inappropriate.
- For the patient who continues to have significant dyspnea despite dual or triple therapy, consider investigating and treating other causes of dyspnea.[1]

Last, keep in mind that *evidence is limited* regarding escalating the dosage of these agents (1) beyond what is listed in **TABLE 2**[1] and (2) in specific instances mentioned in the discussion of each inhaler class. **JFP**

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