Chronic Obstructive Pulmonary Disease (COPD) Agents

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Executive Summary:

- Agent and inhaler device selection within each class should be individualized. Choice is guided by symptom severity, exacerbation risk, side effects, comorbidities, drug availability and cost/insurance coverage, as well as patient's response, preference and ability to use various delivery devices.
- All patients should be offered a short-acting bronchodilator (beta-2 agonist, antimuscarinic or combination) to use as needed for immediate symptom relief. Combination SABA+SAMA products are superior to either medication along in improving FEV1* and symptoms.
- Long-acting muscarinic antagonist (LAMA) is the preferred drug class in patients with moderate to very severe COPD. Clinical trials have shown a greater reduction in exacerbations and hospitalizations for LAMAs (tiotropium) versus long-acting beta agonists (LABAs).
- LAMA and LABA combination devices have significantly greater improvement in lung function compared to LAMA or LABA monotherapy
- Patients with blood eosinophil counts > 300 cells/ mcL will obtain the greatest benefit from inhaled corticosteroids (ICS) therapy. ICS-containing regimens are not beneficial in patients with blood eosinophil counts < 100 cells/mcL.

COMMONLY USED MAINTENANCE MEDICATIONS IN COPD

Beta2-agonists

- **SABAs Effect:** Short-acting beta2-agonists (SABAs) have an effect that lasts about 4 to 6 hours.
- **LABAs Effect:** Long-acting beta2-agonists (LABAs) last about 12 or more hours.
- Beta2-agonists haven't shown a mortality benefit, but do significantly improve forced expiratory volume in the first second (FEV1)* and symptoms.
- **Cardiovascular Notes:** Over stimulation of beta2-adrenergic receptors can produce resting sinus tachycardia and tremors and has the potential to precipitate cardiac rhythm disturbances in susceptible patients. Hypokalemia can occur, especially in combination with thiazide diuretics. Moreover, tachyphylaxis is possible in patients with congestive heart failure (CHF) when oxygen consumption is increased under resting conditions with overuse.

Antimuscarinics

- **Ipratropium** → A systematic review of randomized controlled trials concluded that ipratropium, a short-acting muscarinic antagonist (SAMA), alone provided small benefits over SABAs in terms of lung function, health status, and requirement for oral steroids.
- **LAMA Treatment** → Long-acting antimuscarinic antagonists (LAMAs) treatments improve symptoms and health status. They also improve efficacy of pulmonary rehabilitation and reduce exacerbations and related hospitalizations. Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment versus LABA treatment.
  - LAMA is the *preferred* drug class in patients with moderate to very severe COPD. Clinical trials have shown a greater reduction in exacerbations and hospitalizations for LAMAs (tiotropium) versus LABAs.
  - **Side Effects:** The main side effect is *dryness of mouth*, although some patients using ipratropium report a bitter, metallic taste. Use of solutions with a facemask can precipitate acute glaucoma, likely a direct result of contact between the solution and the eye.

Combination Bronchodilators

- Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with lower risk of side effects compared to increasing the dose of a single bronchodilator.
- SABA/SAMA combination products are superior to either medication alone in improving FEV1* and symptoms.
- There are numerous combinations of LAMA and LABA in a single delivery device available which have significantly greater improvement in lung function compared to LAMA or LABA monotherapy.
- **Dosing:** A lower-dose and twice-daily LAMA/LABA regimen has been shown to improve symptoms and health status in COPD patients compared to monotherapy.
- **Combination vs. Monotherapy:** combination of LAMA/LABA or LAMA/ICS products have a greater effect on symptoms, exacerbations and health status compared to their individual components as monotherapy.
  - **LAMA+LABA Combo Therapy** is recommended for severe COPD in patients who are highly symptomatic. Studies involving patient-related outcomes suggest improved response compared to single agents.
  - **LABA+ICS Combo Therapy** should be reserved for select patients who may benefit due to higher risk of pneumonia and side effects. Patients with asthma or blood eosinophils > 300 cells/microliter may benefit from ICS.

***FEV1** = Forced Expiratory Volume 1 or volume of air forcefully expired in initial 1 second of expiration. A standard measure used to assess severity of obstruction in asthma or COPD.

Inhaled Corticosteroids (ICS)

- In vitro evidence suggests that COPD-associated inflammation has limited responsiveness to corticosteroids. The clinical relevance of this effect has not been established.
- **ICS Alone** → Regular treatment with ICS alone does not modify the long-term decline of FEV1 nor mortality in patients with COPD.
- **ICS + LABA Combination** → In patients with moderate to severe COPD and exacerbations, a combination of ICS/LABA product is more effective than either component alone in improving lung function, health status and reducing exacerbations. ICS/LABA fixed dose combination therapy has shown better reduction in exacerbation rates over LABA alone.
- **Blood Eosinophil Count** → Several studies have shown that blood eosinophil counts predict the magnitude of effect of ICS therapy in preventing exacerbations. Almost no effect is observed at low blood eosinophil counts, while incrementally increasing effect is observed with higher eosinophil counts.
  - ICS-containing regimens are not beneficial in patients with blood eosinophil counts < 100 cells/mcL.
  - Patients with blood eosinophil counts > 300 cells/mcL will obtain the greatest benefit from ICS therapy. The use of blood eosinophil count to predict ICS effect should always be combined with clinical assessment of exacerbation risk.
- **Adverse Effects** → ICS use is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia.

Triple Therapy

- **Fixed-dose Triple vs. LAMA/LABA Combination** → Fixed-dose triple inhaled therapy has been shown to have a mortality benefit versus fixed-dose LAMA/LABA combinations in patients with symptomatic COPD with a history of frequent and/or severe exacerbations.

Phosphodiesterase-4 Inhibitors

- Reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.
- **Roflumilst Benefits** → Roflumilast (e.g., Daliresp®) reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations. The benefits of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation.
- **Adverse Effects** → More adverse effects than inhaled medications for COPD, including diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbances, and headache. Adverse effects tend to occur early in therapy and diminish over time with continued treatment. Roflumilast should also be used with caution in patients with depression as it can increase anxiety, thoughts of suicide and emotional instability.

Antibiotics

Antibiotics & Exacerbation Rates → Recent studies have shown regular use of certain antibiotics may reduce exacerbation rates.

- **Azithromycin**, **Erythromycin**
  - Azithromycin (250 mg/day or 500 mg 3x/week) and erythromycin (250 mg 2x/day) for one year in patients prone to exacerbations reduced the risk of exacerbations compared to usual care.
  - Azithromycin use was associated with higher rates of bacterial resistance, QTc interval prolongation, and impaired hearing tests. There is no data showing the efficacy of prolonging azithromycin use beyond one year in preventing COPD exacerbations.

Methylxanthines

- **Methylxanthines** → May act as non-selective phosphodiesterase inhibitors, however, they also have an extensive range of non-bronchodilator actions.
- Theophylline is metabolized by the cytochrome P-450 pathway and clearance declines with age. There is evidence of a modest bronchodilator effect compared to placebo in stable COPD. Addition of theophylline to salmeterol produces a greater improvement in FEV1 and less shortness of breath than salmeterol alone.
- **Adverse Effects** → Events include development of arrhythmias, palpitations, and seizures. More minor side effects include headaches, insomnia, nausea, and heartburn. These medications also have a wide variety of drug-drug interactions.

***FEV1** = Forced Expiratory Volume 1 or volume of air forcefully expired in initial 1 second of expiration. A standard measure used to assess severity of obstruction in asthma or COPD.

Common Inhalers for COPD Management

Generic Name	Brand Name	Generic Available	Inhaler Type	Typical Dosing
Beta2-Agonists (Bronchodilators)				
Short-acting (SABA)				
Levalbuterol	Xopenex HFA®	Yes	MDI	1-2 puffs q4-6h PRN
Albuterol	Proair® HFA, Proair RespiClick®, Proventil® HFA, Ventolin® HFA	Yes	MDI, DPI	1-2 puffs q4-6h PRN
Long-acting (LABA)				
Salmeterol xinafoate	Serevent®	No	DPI	1 inhalation BID
Formoterol	Foradil Aerolizer®	No	DPI	1 inhalation/neb BID
Formoterol	Performist®	Yes	Neb	
Arformoterol	Brovana®	No	Neb	1 inhalation/neb BID
Olodaterol	Striverdi Respimat®	No	SMI	1 inhalation daily
Anticholinergics (Bronchodilators)				
Short-acting (SAMA)				
Ipratropium	Atrovent® HFA	No	MDI	2 inhalations 4XD
Long-acting (LAMA)				
Tiotropium	Spiriva® HandiHaler® Spiriva® Respimat®	No	DPI SMI	Inhale 1 capsule BID 2 inhalations daily
Umeclidinium	Incruse® Ellipta®	No	DPI	1 inhalation daily
Aclidinium bromide	Tudorza Genuair	No	DPI	1 inhalation BID
Revefenacin	Yupelri®	No	Neb	1 nebulization daily
Glycopyrronium bromide	Seebri® Breezhaler®	No	DPI	Inhale 1 capsule daily
Combination Products				
SABA+SAMA				
Ipratropium/albuterol	Combivent® Respimat®	Yes (nebs only)	SMI	1 inhalation 4XD
LAMA+LABA				
Umeclidinium/Vilanterol	Anoro® Ellipta®	No	DPI	1 inhalation daily
Olodaterol/Tiotropium	Stiolto Respimat®	No	SMI	1 inhalation daily
Formoterol/Glycopyrronium	Bevespi Aerosphere®	No	MDI	1 inhalation BID
Formoterol/Aclidiunium	Duaklir Pressair®	No	DPI	1 inhalation BID
ICS+LABA				
Budesonide/Formoterol	Symbicort®	Yes	MDI	2 inhalations BID
Fluticasone/Salmeterol	Advair®, AirDuo®, Wixela™, Inhub™	Yes	DPI	1 inhalation BID
Fluticasone/Vilanterol	Breo™ Ellipta™	No	DPI	1 inhalation daily
Formoterol/Mometasone	Dulera®	No	MDI	2 inhalations BID
ICS+LAMA+LABA				
Fluticasone/Umeclidinium/ Vilanterol	Trelegy™ Ellipta®	No	DPI	1 inhalation daily

Budesonide/Formoterol/ Glycopyrrolate	Breztri Aerosphere®	No	MDI	2 inhalations BID
Phosphodiesterase-4 Inhibitors				
Roflumilast	Daliresp®	No	Tablet	1 tab daily x 4 weeks, then 2 tabs daily
Methylxanthines				
Theophylline	Theo-24	Yes	Tablet/Capsule	Titrate to effect
Aminophylline		Yes	IV	Titrate to effect

DPI – Dry Powdered Inhaler; **MDI** – Metered Dose Inhaler; **SMI** – Soft Mist Inhaler; **Neb** - Nebulizer

References:

1. 2021 GOLD Reports. Global Initiative for Chronic Obstructive Lung Disease - GOLD.. Accessed February 23, 2022.

Uncontrolled Chronic Obstructive Pulmonary Disease (COPD)

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Executive Summary

The initiation of COPD therapy is determined by the patients' individualized symptoms, exacerbation risk and the use of an assessment tool such as the mMRC dyspnea scale or CAT assessment. Follow-up therapy is determined by persistent dyspnea and/or further exacerbations, and the patient's current COPD treatment.

Key Updates and Takeaways

- The 2023 GOLD guideline updates reflect a change in the initial therapy and assessment tool (Table 1).
- Group E was created to recognize the clinical relevance of exacerbations regardless of the level of patient symptoms.
- Group B treatment was adjusted to promote combination long-acting bronchodilator based on evidence showing the combination was superior to a LAMA in this group.
- ICS is only recommended in those with exacerbations with elevated blood eos.
- Follow-up management is guided based on how the patient presents, by dyspnea or exacerbations.

Acronyms	
CAT	COPD Assessment Test
COPD	Chronic Obstructive Lung Disease
eos	Blood eosinophil count in cell per microliter (µL)
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled corticosteroid
LABA	Long-acting beta agonist
LAMA	Long-acting antimuscarinic
mMRC	Modified Medical Research Council Dyspnea Questionnaire
SABA	Short-acting beta agonist
SAMA	Short-acting antimuscarinic

Table 1: Initial Therapy for COPD

	mMRC 0-1, or CAT < 10 (less symptomatic)	mMRC ≥ 2, or CAT ≥ 10 (more symptomatic)
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** Bronchodilator (short-acting or long-acting bronchodilator)	**Group B** LABA + LAMA*
≥ 2 moderate exacerbations, or ≥ 1 exacerbation leading to hospitalization per year	**Group E** LABA + LAMA* Consider LABA+LAMA+ICS* if blood eos ≥ 300	

*single inhaler therapy may be more convenient and effective than multiple inhalers

Table 2: mMRC Dyspnea Questionnaire

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house, or I am breathless while dressing

TIP: COPD Assessment Test (CAT) can be found on the Guidelines and Algorithms KnowledgeNet page under "Pharmacy Pearls."

Overview of Changes with GOLD 2023 Guidelines

Initial Assessment Tool

- Replacement of the ABCD initial assessment tool with a new ABE model (Table 1)
    - Group E merges the previous Group C and D to recognize the clinical relevance of exacerbations, independent of the level of symptoms
    - Group B
        - LABA + LAMA was shown to be superior to a LAMA in patients with more symptoms and ≤ 1 moderate exacerbation in the prior year in regards to early and sustained improvements in lung function and symptoms, and reduces the risk of deterioration and/or treatment failure
        - If a LABA + LAMA combination is not considered appropriate, there is no evidence to recommend one class over the other
    - Group A remains unchanged
        - If available and affordable, a long-acting bronchodilator is the preferred choice
        - Consider a short-acting bronchodilator in patients with very occasional breathlessness
- LABA + ICS removed from initial treatment algorithmBlood eos > 300 cells/µL with exacerbations
    - Triple therapy has been shown to reduce future exacerbations, COPD-related health care resource utilization and mortality

Follow-up Treatment Algorithm

- LABA + ICS removed from follow-up treatment algorithm
    - LABA + ICS should be continued in patients who are already on treatment with stable disease
    - Escalation to other therapies should be considered for patients who have further exacerbations or major symptoms

Table 3: When to Start an Inhaled Corticosteroid

Strong Support to Use if:	• The patient has a history of hospitalizations for exacerbations • 2 or more moderate exacerbations per year despite long-acting bronchodilator therapy • Blood eos > 300 cells/µL • A history of asthma
Consider Use if:	• 1 moderate exacerbation of COPD per year despite long-acting bronchodilator therapy • Blood eos 100 to < 300 cells/µL
Do Not Use if:	• The patient has repeated pneumonia events • Blood eos < 100 cells/µL • A history of mycobacterial infection

Follow-up Management

When following up on a patient's COPD medications, the review, assess and adjust method should be utilized.

- **Review** the patient's dyspnea symptoms and exacerbation risk.
- **Assess** the patient's inhaler technique, adherence and non-pharmacological approaches.
- **Adjust** pharmacological treatment accordingly. If dyspnea or exacerbation risk is identified, consider the following adjustments.

Dyspnea

For patients with persistent breathlessness or exercise limitation on current treatment, recommend adjusting treatment as outlined below.

Table 4: Dyspnea Treatment Adjustments

Current Treatment	Adjust to
Bronchodilator monotherapy	LABA + LAMA
LABA + LAMA	Switch inhaler device or molecule Implement or escalate non-pharmacologic treatment(s) Investigate (and treat) other causes of dyspnea
LABA + ICS	LABA + LAMA (if patient has no features of asthma) LABA + LAMA + ICS (if patient has concomitant asthma, or history of exacerbations + elevated blood eos)

Exacerbations

For patients who develop further exacerbations with or without dyspnea on current treatment, recommend adjusting treatment as outlined below.

Table 5: Exacerbation Treatment Adjustments

Current treatment	Adjust to	
Bronchodilator monotherapy	If blood eos <300 → LABA + LAMA	
	If blood eos ≥300 → LABA + LAMA + ICS	
LABA + LAMA	If blood eos <100 →	If FEV1 <50% and chronic bronchitis → add roflumilast
		Former smoker → add azithromycin
	If blood eos ≥100 → LABA + LAMA +ICS	
LABA + ICS	LABA + LAMA + ICS	
LABA + LAMA + ICS	If FEV1 <50% and chronic bronchitis → add roflumilast	
	Former smoker → add azithromycin	

References

Tamondong-Lachica DR, Skolnik N, Hurst JR, et al. GOLD 2023 Update: Implications for Clinical Practice. *International Journal of Chronic Obstructive Pulmonary Disease*. 2023;18:745-54.

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