LAMAs Across COPD and Asthma: Practical Escalation Strategies With a Sustainability Lens

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doi:10.12788/fp.0788

Sponsorship: This activity is sponsored by Primary Care Education Consortium and Primary Care Respiratory Group and supported by funding from AstraZeneca.

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DISCLOSURES

Dr. Solis is on the advisory board of and is a speaker and researcher for AstraZeneca.

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, at Primary Care Education Consortium.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and asthma remain major public health issues in the United States and present a substantial clinical burden for patients.[1,2] In 2023, the age-adjusted prevalence of diagnosed COPD in adults was approximately 3.8%, and in 2024 about 4.2% of adults were diagnosed with COPD, emphysema, or chronic bronchitis.[2,3] The prevalence of asthma in 2024 was estimated at 8.6% of adults and 6.5% of children.[1,4] In both COPD and asthma, certain populations experience disproportionate disease burden. National surveillance data show persistent disparities in the prevalence of COPD among people who smoke, older adults, and those living in rural communities.[2,3] In an analysis of asthma trends, prevalence increased among adults from 2013 through 2021 and remained disproportionately high among non-Hispanic Black children and adults (12.5% and 10.6%, respectively) compared with non-Hispanic White children and adults (5.7% and 8.2%).[4]

Uncontrolled disease remains common after diagnosis for both COPD and asthma. In a US study of patients newly diagnosed with COPD, only about 36% received maintenance therapy, underscoring undertreatment early in the disease course.[5] In severe asthma, observational studies indicate that approximately 35% to 51% of US patients with evidence of uncontrolled disease had no specialist visit or medication escalation afterward, despite the risk of future exacerbations and health care use.[6,7] Exacerbations remain a dominant driver of morbidity in both COPD and asthma. For COPD, poor adherence to inhaled therapy was associated with a 40% higher exacerbation risk in a 2024 meta-analysis.[8] For asthma, recent claims analyses show increased costs among patients who remain uncontrolled while on long-acting beta$_2$-agonist (LABA) and inhaled corticosteroid (ICS) maintenance therapy.[6,9]

The economic burden for these airway diseases is substantial. A 2023 US analysis estimated annual COPD-specific direct costs at $24.0 billion, with prescription drugs contributing $10.5 billion; national projections estimate that COPD-attributable medical costs will rise to $60.5 billion by 2029.[10,11] For asthma, the economic burden is estimated at approximately $50 billion in direct medical costs and $32 billion in

Key takeaways

- Long-acting muscarinic antagonists (LAMAs) occupy a central role in care for COPD and asthma. In COPD, they are foundational bronchodilators from initial treatment onward; LAMAs are add-on therapy for patients with asthma whose disease remains uncontrolled despite optimized ICS-based treatment.
- In COPD, LAMAs improve bronchodilation, mucus biology, small-airway physiology, and airway remodeling pathways and reduce exacerbations. Dual LABA/LAMA combinations are preferred for many symptomatic patients; triple therapy is used when exacerbation risk and eosinophilic disease indicate the addition of ICS would be helpful.
- In asthma, escalation to LAMA-containing regimens improves lung function and can reduce exacerbations in selected patients, although biologics should still be considered in those with severe type 2–driven disease.
- Sustainability in chronic airway disease is an increasingly important consideration, but it should reinforce rather than override clinical judgment. The most environmentally responsible inhaler is the one that the patient can use correctly and consistently while maintaining disease control.

indirect and mortality-related costs in the United States.[12] Furthermore, uncontrolled symptoms and health care utilization are linked to undertreatment, nonadherence, and shortcomings in care delivery in asthma and COPD.[13,14]

LAMAs play a key role in improving disease control and reducing burden for certain patients with COPD and/or asthma.[13,14] In COPD, the Global Initiative for Obstructive Lung Disease (GOLD) 2026 recommendations place LAMAs in initial and follow-up pharmacotherapy algorithms, either alone or as part of dual and triple therapy (GOLD Groups B and E).[14] Additionally, LAMA monotherapy has shown a lower incidence of exacerbation and nonserious adverse events than LABA monotherapy.[15] In asthma, a meaningful proportion of patients remain uncontrolled even when adherent to ICS/LABA, supporting step-up strategies. The Global Initiative for Asthma (GINA) recommends LAMAs for patients who remain uncontrolled on at least medium-dose ICS/LABA, positioning them as an inhaled therapy escalation before or alongside specialist-directed severe asthma evaluation.[13] LAMAs also improve lung function in patients with asthma and asthma-COPD overlap.[16,17]

MECHANISTIC RATIONALE FOR LAMAs

The mechanistic rationale for LAMAs in both COPD and asthma is understood in the context of acetylcholine signaling and muscarinic acetylcholine receptors, especially the M3 subtype.[18,19] Parasympathetic cholinergic signaling contributes directly to airway smooth-muscle contraction, mucus secretion, and increased bronchomotor tone in obstructive airway disease, with the muscarinic M3 receptor playing an important role in bronchoconstriction.[19] LAMAs provide prolonged bronchoprotection by antagonizing muscarinic signaling, particularly at the M3 receptor, addressing one of the most consistent reversible components of airflow obstruction.[18,19]

Muscarinic biology also extends beyond airway smooth muscle. Preclinical data show that tiotropium inhibits and can reverse interleukin-13–induced goblet cell metaplasia in human airway epithelial cells, supporting the clinical observation that antimuscarinic therapy may help temper mucus-related morbidity as well as bronchospasm.[20] Additional translational evidence further suggests anti-inflammatory and antifibrotic effects that may complement bronchodilation.[19,21] A 2025 position paper by the European Academy of Allergy and Clinical Immunology notes that LAMAs influence muscarinic pathways in airway smooth muscle, epithelial cells, and inflammatory cells, supporting their value in phenotypes marked by persistent bronchoconstriction and mucus hypersecretion.[21] In practical terms, LAMAs connect pharmacology with physiology because activation of the cholinergic pathway narrows airways, amplifies reflex bronchomotor tone, and contributes to mucus-related obstruction. Blocking this pathway has multiple complementary effects: relaxation of airway smooth muscle, improved airway caliber, less mucus-driven plugging, and potential moderation of remodeling signals that sustain chronic airflow limitation.[18-21] This helps explain why LAMA benefits can appear clinically as improved forced expiratory volume in 1 second (FEV_1), reduced rescue therapy use, improved symptoms, and fewer exacerbations rather than simply as a short-term bronchodilator response.[13,14]

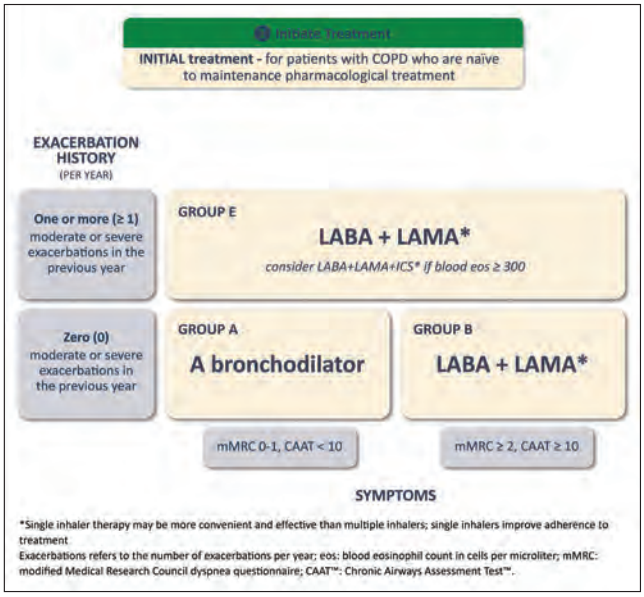
In COPD, LAMA use results in reduced sputum production, goblet cell differentiation, and hyperplasia. Muscarinic blockade can be the backbone of maintenance therapy because bronchodilation is a core treatment target in COPD, whereas in asthma these same benefits are most useful as an adjunct to ICS.[13,14,22]

CLINICAL USE OF LAMAs IN COPD

GOLD 2026 recommendations place LAMAs at the center of COPD pharmacotherapy. For initial treatment, patients in GOLD Group A may start with any bronchodilator (LAMA or LABA), but patients in GOLD Group B are recommended to receive LABA/LAMA dual therapy, and patients in GOLD Group E should also receive LABA/LAMA, with consideration of LABA/LAMA/ICS when blood eosinophils are at least 300 cells/μL (**FIGURE 1**).[14] LAMA monotherapy remains clinically relevant in COPD, particularly for symptomatic patients with a lower exacerbation burden or for those beginning maintenance therapy.[14] In a 2020 systematic review and meta-analysis, LAMA therapy produced a lower incidence of exacerbation and nonserious adverse events than LABA monotherapy and delivered higher FEV_1.[15] The long-term UPLIFT trial similarly showed that tiotropium improved lung function, health-related quality of life, and exacerbation outcomes over 4 years.[23] Of note, both LAMA and LABA monotherapy improve lung function, symptoms, health status, exercise tolerance, and exacerbations in COPD, and GOLD does not prefer one over the other for patients in GOLD Group A.[14] Data suggest that LAMAs may be preferred for exacerbation prevention and some experts propose that LABAs may be preferred for symptom reduction.[24] In a recent US analysis, LAMA monotherapy was prescribed more often in patients with COPD (23.5%) than LABA monotherapy (1.7%).[5]

When symptoms persist and/or in the event of a moderate or severe exacerbation, the escalation after inhaled monotherapy is usually dual bronchodilation rather than switching to a different monotherapy.[14] Meta-analysis data note that LABA/LAMA dual therapy is superior to either LABA or LAMA monotherapy for symptomatic COPD, with lower risks of exacerbations and hospitalizations and no signal for more treatment-emergent adverse effects.[25] Among fixed-dose combinations, head-to-head and comparative analyses also show that dual bronchodilation can improve lung function and rescue-medication use beyond what is achieved with single bronchodilators alone.[26]

FIGURE 1. GOLD recommendations for initial pharmacologic therapy for COPD.[14]



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The LAMA component remains important even when treatment advances to triple therapy. For patients with continued exacerbations on bronchodilator monotherapy or dual therapy, GOLD recommendations consider exacerbation history and blood eosinophils to determine whether escalation to an ICS-containing regimen is warranted and if LAMAs remain part of that intensified strategy (**FIGURE 2**).[14] Of note, many patients still receive legacy LABA/ICS regimens, which are no longer recommended for COPD.[5,14]

Patient selection for LAMA-based therapy includes factors such as symptom burden, prior exacerbations, comorbid cardiovascular disease, inhaler technique, cognitive or physical limitations, and likelihood of adherence, some of which determine GOLD Group and therapy progression based on GOLD algorithms.[8,14] Of note, a 2025 meta-analysis showed significant trough FEV_1 improvement with LAMAs vs placebo and suggested that older adults with COPD may derive at least comparable, and possibly greater, benefit from once-daily LAMA treatment as younger patients.[18] In COPD, clinicians can pair symptom scores, such as the COPD Assessment Test (CAT) or modified Medical Research Council scale, with exacerbations, rescue medication use, adherence and technique checks, spirometry, and blood eosinophils when ICS escalation is being considered.[14] Electronic medical record questionnaires or visit templates can make these data easier to visualize across encounters. For patients with frequent exacerbations, rapidly declining lung function, diagnostic uncertainty, or persistent symptoms despite optimized bronchodilation, clinicians should promptly collaborate with pulmonology or other relevant specialists.[14]

Device selection plays an important role in effective therapy for COPD. Single-inhaler therapy may be more convenient and effective than multiple inhalers because it can improve adherence, and guideline-directed follow-up includes switching device or molecules when dyspnea persists despite appropriate treatment.[14] The best COPD regimen is the one that matches the patient's inspiratory ability, dexterity, routine, and willingness to use it consistently.[8,14] In COPD, LAMAs are a core therapeutic component across monotherapy, dual-therapy, and triple-therapy regimens.

CLINICAL USE OF LAMAs IN ASTHMA

The role of LAMAs in asthma is somewhat more selective than in COPD, but their role in therapy has been increasingly established. GINA recommends considering a LAMA as add-on therapy for adults and adolescents whose asthma remains uncontrolled despite maintenance ICS/LABA at Step 5, after adherence, inhaler technique, comorbidities, and modifiable risk factors have been reassessed (**FIGURE 3**).[13]

Classic trial evidence for LAMAs in asthma comes from

FIGURE 2. GOLD recommendations for follow-up pharmacologic therapy for COPD.[14]

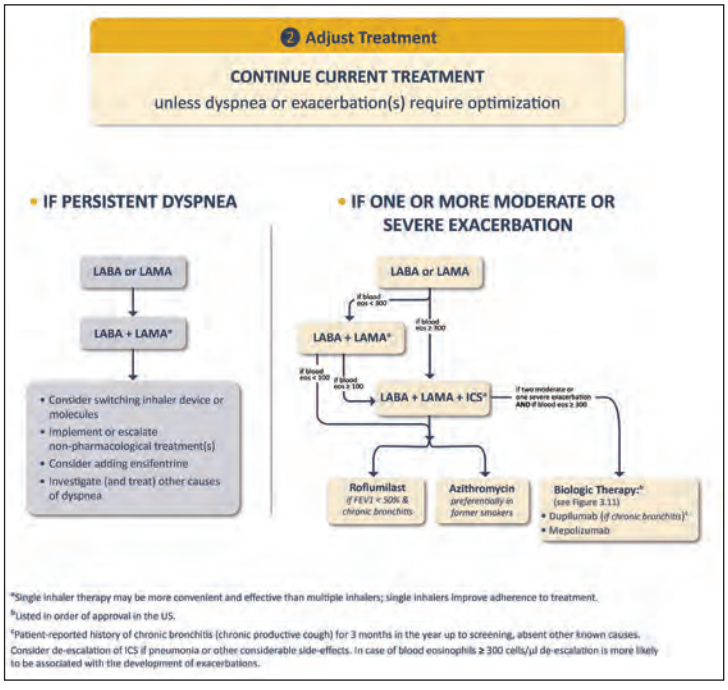

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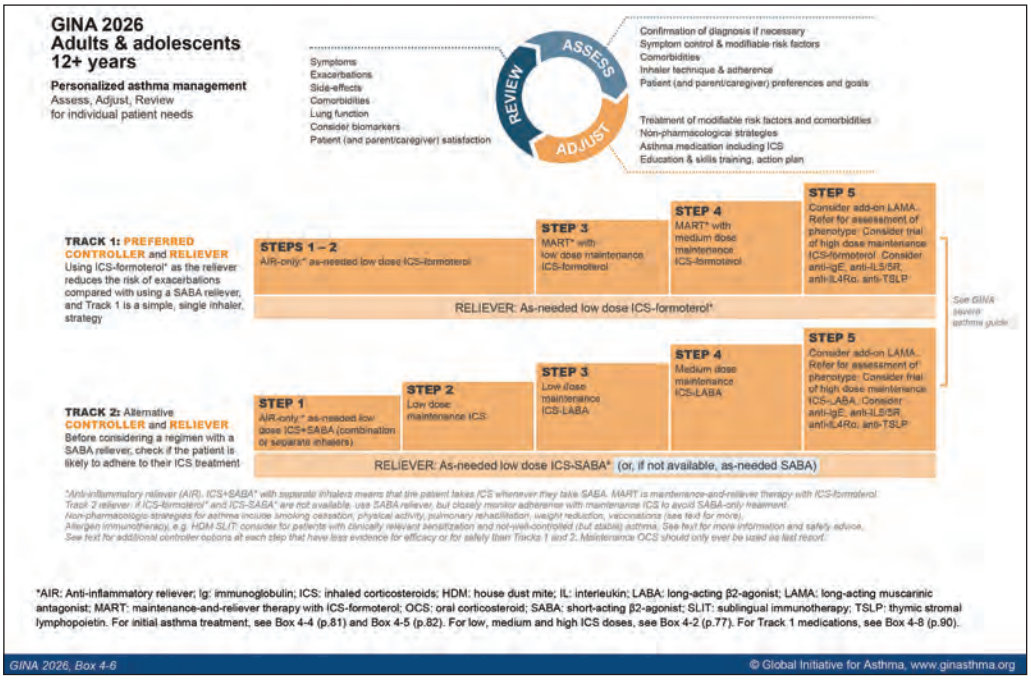
FIGURE 3. GINA recommendations for asthma treatment steps in adults and adolescents.[13]



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tiotropium studies.[27,28] In adults with asthma poorly controlled on ICS/LABA, add-on tiotropium increased the time to first severe exacerbation from 226 days to 282 days and reduced the overall risk of severe exacerbation by 21% (hazard ratio, 0.79, P=.03).[28] A Cochrane review likewise found that adding a LAMA to ICS lowered the odds of exacerbations requiring oral corticosteroids vs the same ICS dose alone, with an odds ratio of 0.65 (95% confidence interval [CI]: 0.46, 0.93).[27]

More recent evidence has expanded the LAMA role in asthma from tiotropium add-on therapy to single-inhaler triple therapy. In IRIDIUM, both high- and medium-dose mometasone/indacaterol/glycopyrronium significantly improved trough FEV_1 vs the corresponding ICS/LABA comparator, with between-group gains of 65 mL and 76 mL at week 26.[16] In TRIMARAN and TRIGGER, extrafine beclomethasone/formoterol/glycopyrronium reduced severe exacerbations over 52 weeks in adults with uncontrolled asthma receiving ICS/LABA.[29] Other phase 3 trials show similar benefits of LAMAs as part of triple inhaled therapy for asthma. The ARGON study showed that once-daily indacaterol/glycopyrronium/mometasone provided noninferior quality-of-life improvement vs high-dose salmeterol/fluticasone plus tiotropium.[30] CAPTAIN showed that adding umeclidinium to fluticasone furoate/vilanterol improved lung function in inadequately controlled disease.[31]

KALOS and LOGOS were large phase 3 trials that provide data for single-inhaler triple therapy in asthma. These replicate, randomized, double-blind trials enrolled adolescents and adults with asthma that remained inadequately controlled despite medium- or high-dose ICS/LABA and compared budesonide/glycopyrronium/formoterol (BGF) with dual budesonide/formoterol comparators over 24 to 52 weeks.[32] There were 2 BGF groups: BGF 28.8 (BGF 320 µg, 28.8 µg, 10 µg) and BGF 14.4 (BGF 320 µg, 14.4 µg, 10 µg). In pooled analyses, BGF 28.8 improved morning pre-dose trough FEV_1 by 76 mL and FEV_1 area under the curve from 0 hours to 3 hours by 90 mL over 24 weeks vs combined ICS/LABA comparators, and it reduced severe exacerbations by 14% (incidence rate ratio, 0.86; 95% CI: 0.76, 0.97).[32] Safety was broadly similar across treatment groups, and no deaths were considered treatment-related.

A meta-analysis of triple vs dual inhaled therapy showed better lung function and fewer severe exacerbations, but gains were generally smaller than those seen with biologics in carefully phenotyped severe type 2 asthma.[33] Accordingly, GINA places LAMA add-on therapy and biologics in the same step (Step 5), although these therapies are not interchangeable and treatment selection depends on patient characteristics.[13,34]

In practice, the patients most likely to benefit from a LAMA are those with persistent symptoms or exacerbations despite optimized ICS/LABA, especially when airflow limitation remains evident and bronchoconstriction appears to be a major contributor to impairment.[13,21] Single-inhaler triple therapy may also be attractive for patients whose disease is uncontrolled in part due to regimen complexity; US real-world data show better adherence and persistence with single-inhaler vs multiple-inhaler triple therapy.[13,35] For many patients, adding a LAMA represents an option for inhaled therapy escalation before biologic initiation; single-inhaler triple therapy can be a useful adjunct even after specialist referral, particularly when the goal is to improve lung function, simplify inhaled therapy, and reduce exacerbation risk without moving immediately to injectable treatment.[13,35]

TABLE 1. Key considerations for LAMA use in COPD and asthma.[13,14]

Domain	COPD	Asthma
Guideline placement	Foundational bronchodilator across initial and follow-up treatment	Add-on therapy for uncontrolled disease despite ICS/LABA (Step 5)
Typical escalation trigger	Persistent dyspnea or exacerbations prompt movement from LAMA to LABA/LAMA or LABA/LAMA/ICS depending on eosinophils	Persistent symptoms or exacerbations after optimization of adherence, technique, and comorbidity management
Potential benefits	Improved FEV_1, dyspnea, and health status plus exacerbation reduction[15,23]	Improved lung function and selected exacerbation outcomes, especially with add-on or single-inhaler triple therapy[16,28]
Illustrative data	LAMA lowered exacerbation incidence vs LABA in meta-analysis; tiotropium outperformed salmeterol for exacerbation prevention[15,36]	Tiotropium extended time to first severe exacerbation to 282 vs 226 days; improved trough FEV_1 by 65 to 76 mL[16,28]
Device strategy	Choose regimen and device according to symptoms, exacerbation history, dexterity, and adherence likelihood; single inhaler often preferred when possible[8,14]	Align device with technique and treatment complexity; single-inhaler triple therapy improves adherence vs multiple inhalers[13,35]
Sustainability lens	Preventing COPD exacerbations is environmentally meaningful because health care utilization carries a carbon burden[37,38]	Device switches should not compromise control; clinical fit and correct use remain the first priorities[39,40]

Structured reassessment can improve escalation decisions in asthma. For example, clinicians can confirm adherence and inhaler technique, use validated questionnaires such as the Asthma Control Test (ACT) or Asthma Impairment and Risk Questionnaire (AIRQ), review exacerbation and oral corticosteroid history, repeat spirometry when control is uncertain, and evaluate type 2 biomarkers, such as blood eosinophils or fractional exhaled nitric oxide, when severe asthma or biologic eligibility is being considered.[13] This approach may help clinicians clarify whether the next move should be escalation to LAMA-containing inhaled therapy, biologic evaluation, specialist referral, or additional workup for comorbidities and alternative diagnoses.[13]

Clinical considerations for the use of LAMAs in COPD and asthma as discussed in this article are described in **TABLE 1**.

SUSTAINABILITY IN RESPIRATORY CARE

Sustainability is increasingly recognized as a component of respiratory care due to the environmental footprint of inhalers and health care utilization (e.g., emergency visits, hospitalizations).[37,41] The clinically relevant application of sustainability is that poor disease control can be environmentally costly and medically harmful, because increased health care utilization carries a carbon burden; therefore, preventing exacerbations is a high-impact strategy to potentially reduce the system-level carbon footprint of care.[37,38]

Studies have estimated the environmental impact of airway disease–related care. In a 2025 serial cross-sectional US analysis, 1.6 billion inhalers dispensed from 2014 to 2024 generated an estimated 24.9 million metric tons of carbon dioxide emissions, with metered-dose inhalers responsible for 98% of emissions.[41] After the 2021 US Department of Veterans Affairs formulary transition from budesonide–formoterol metered-dose inhaler to fluticasone–salmeterol dry-powder inhaler to reduce propellant use, most facilities switched more than 80% of patients, with 14.2% later switching back.[42] The subsequent outcomes study associated the original transition from metered-dose inhalers to dry-powder inhalers with increased hospital-based utilization; these findings may reflect health-system–specific implementation factors and may not be generalizable to all switching approaches.[39]

For clinicians, a practical sustainability principle may be summarized as "best for the patient first, then the planet."[13,40] Shared decision-making should include consideration of access, likelihood of correct use, treatment goals, inhaler continuity, and environmental impact rather than carbon metrics alone. This is particularly relevant for LAMA-containing regimens because they are available across multiple device platforms and as both single- and multiple-inhaler combinations.

Encouragingly, newer propellants may reduce the trade-off between clinical familiarity and environmental performance. HFO-1234ze(E) has been proposed as a near-zero-global-warming-potential propellant for pressurized metered-dose inhalers, and current modeling and nonclinical assessment suggest negligible trifluoroacetic-acid deposition and an acceptable safety profile for continued development.[43,44]

SUMMARY

COPD and asthma continue to impose a major burden in the United States, with substantial prevalence, persistent disparities, frequent uncontrolled disease, ongoing exacerbations, and high health care costs. Many patients remain undertreated after diagnosis or continue to have poor control despite maintenance therapy, which contributes to future exacerbations,

greater health care utilization, and rising economic and environmental impact. LAMAs help address these gaps by targeting cholinergic bronchoconstriction and related mucus and inflammatory pathways, making them a central part of COPD management and a useful step-up option in asthma. Their clinical value depends not only on efficacy, but also on selecting the right regimen and device for the individual patient to support adherence. Sustainability considerations increasingly favor approaches that improve control and prevent exacerbations while minimizing avoidable environmental impact. ●

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