

COPD: Why one moderate exacerbation changes everything

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Chronic obstructive pulmonary disease (COPD) management often involves a delicate balance between symptom control and exacerbation prevention. For many patients, dual bronchodilator therapy (LAMA/LABA) provides adequate relief, but the trajectory of the disease is rarely linear. The question for clinicians then becomes: at what point does a patient's clinical picture warrant a more aggressive approach, specifically moving to a single-inhaler triple therapy (SITT)?

KEY TAKEAWAYS

- **The Pivot:** A single moderate COPD exacerbation, even on dual bronchodilator therapy, indicates a need to re-evaluate and often intensify treatment.
- **The Data:** Triple therapy reduces exacerbation rates and improves lung function compared to dual bronchodilator regimens in appropriate patient groups.
- **The Action:** Consider stepping up to a SITT for patients experiencing one moderate exacerbation while on LAMA/LABA, particularly those with elevated eosinophil counts.

Chronic obstructive pulmonary disease is a progressive, debilitating condition characterized by persistent respiratory symptoms and airflow limitation. Its natural history is punctuated by acute exacerbations, which are critical events that significantly impact quality of life, accelerate lung function decline, and increase mortality risk. Preventing these exacerbations is a cornerstone of effective COPD management, driving treatment decisions from initial diagnosis through advanced stages. Current guidelines generally advocate for a stepwise approach, beginning with bronchodilators and escalating therapy based on symptom burden and exacerbation history. For many patients, a long-acting muscarinic antagonist (LAMA) combined with a long-acting beta-agonist (LABA) in a dual bronchodilator regimen serves as the foundational maintenance therapy.

But the efficacy of dual bronchodilator therapy, while substantial for symptom control, does not universally prevent all exacerbations. Patients with a history of frequent exacerbations, or those with specific inflammatory phenotypes, often require more intensive treatment. The challenge for general practitioners and specialists alike is identifying the precise moment to transition a patient from a seemingly stable dual therapy to a more complex regimen, such as a single-inhaler triple therapy (SITT) which combines a LAMA, a LABA, and an inhaled corticosteroid (ICS). This decision point is not always clear-cut, especially when a patient experiences their first exacerbation while already on dual therapy.

Understanding the Exacerbation Threshold

A moderate COPD exacerbation permanently alters a patient's clinical trajectory, shifting them into a high-risk category for future events and cardiovascular complications. A moderate COPD exacerbation is typically defined by an acute worsening of respiratory symptoms requiring systemic corticosteroids or antibiotics, or both. It does not necessitate hospitalisation, but it represents a significant clinical event. The occurrence of even 1 such moderate exacerbation while a patient is already receiving dual bronchodilator therapy should serve as a strong signal for treatment intensification. This is a departure from older paradigms that might have waited for multiple exacerbations or more severe events before considering triple therapy. The rationale for this earlier intervention stems from the understanding that each exacerbation, regardless of severity, contributes to disease progression and carries a cumulative burden.

The impact of a single event is quantified in a Danish cohort study of 8,453 patients with GOLD B COPD.⁵ Researchers followed patients for 3 years, comparing 4,545 patients with no prior exacerbations against 3,908 patients who had experienced exactly 1 moderate exacerbation in the previous year.⁵ For those with a single prior moderate event, the odds ratio for experiencing 2 or more moderate exacerbations was 2.60, and the odds ratio for a severe exacerbation was 2.08 compared to those with no events.⁵ The same study demonstrated an odds ratio of 1.85 for death in the single-exacerbation group.⁵

This accelerated risk extends beyond respiratory decline to immediate cardiovascular danger. An analysis of the Clinical Practice Research Datalink Aurum database tracked 213,466 patients with COPD in England, recording 40,773 cardiovascular events.⁴ In the 14 to 30 days following a moderate exacerbation, the adjusted hazard ratio for a cardiovascular event was 1.94.⁴ While severe exacerbations drove higher immediate cardiovascular risk, the heightened relative rates of events like heart failure and arrhythmia remained elevated beyond 1 year irrespective of the exacerbation's initial severity.⁴

Retrospective database analyses and observational cohorts do not establish direct causality, as shared underlying vulnerabilities likely drive both respiratory and cardiovascular events. The data lack the granularity to confirm whether preventing the exacerbation would definitively prevent the subsequent stroke or arrhythmia. For clinicians, this reframes the moderate exacerbation from a routine disease fluctuation to a critical intervention window. Preventing subsequent exacerbations becomes paramount, driving the rationale for earlier intervention with therapies that address the inflammatory component of COPD more comprehensively.

The Role of Eosinophils in Treatment Decisions

Blood eosinophil counts dictate whether inhaled corticosteroids will prevent future exacerbations or merely expose the patient to unnecessary side effects. The decision to step up to a single-inhaler triple therapy is not merely about the number of exacerbations, but also about patient characteristics that predict a better response to intervention. Blood eosinophil count has emerged as a biomarker in this context. Patients with higher baseline eosinophil counts are more likely to benefit from the addition of an inhaled corticosteroid to their bronchodilator regimen, as eosinophilic inflammation is often associated with a greater propensity for exacerbations and a better response to the anti-inflammatory effects of corticosteroids.

The predictive value of these clinical characteristics is well documented. A systematic review of 76 studies, comprising 61 observational cohorts and 15 randomized controlled trials, evaluated prognostic risk factors for moderate-to-severe COPD exacerbations.⁶ While 34 studies confirmed that a history of prior exacerbations was the strongest predictor of future events, 16 separate studies identified higher blood eosinophil counts as a significant independent predictor of

future moderate-to-severe exacerbations.⁶

Targeting this specific inflammatory pathway yields measurable clinical benefits. A pre-specified meta-analysis of the 52-week METREX and METREO trials evaluated the biologic mepolizumab in 1,136 patients with COPD who had blood eosinophil counts of 150 cells/ μ L or greater at screening, or 300 cells/ μ L or greater in the prior year.³ Patients received mepolizumab 100 mg subcutaneously or placebo added to existing inhaled corticosteroid-based triple maintenance therapy.³ The biologic reduced the annual rate of moderate to severe exacerbations by 18% (rate ratio 0.82) and delayed the time to the first moderate or severe exacerbation.³

Trials evaluating targeted biologics in highly selected populations already on maximal triple therapy do not directly translate to the initial decision to start an inhaled corticosteroid in a general practice setting. The 52-week duration also leaves the lifelong impact of eosinophil depletion in COPD unmapped. For a patient on dual bronchodilators who experiences a moderate exacerbation, assessing their blood eosinophil count is an important step before initiating triple therapy. If the eosinophil count is low, the benefit of adding a corticosteroid may be less pronounced, whereas a high count strengthens the argument for stepping up to target the right therapy to the right patient.

Mechanism of Action and Clinical Benefits

Single-inhaler triple therapy suppresses both airflow limitation and underlying airway inflammation to reduce exacerbation frequency, though novel mechanisms are required for patients who cannot tolerate corticosteroids.

Single-inhaler triple therapy combines the bronchodilatory effects of a long-acting muscarinic antagonist and a long-acting beta-agonist with the anti-inflammatory action of an inhaled corticosteroid. Muscarinic antagonists block receptors in the airways to reduce mucus secretion, while beta-agonists stimulate beta-2 adrenergic receptors. The combination provides maximal bronchodilation, addressing the airflow limitation central to COPD, while the addition of a potent anti-inflammatory agent aims to provide superior symptom control and reduce the frequency of exacerbations compared to dual therapy alone.

The convenience of a single inhaler for all 3 medications simplifies the treatment schedule, potentially improving patient compliance and clinical outcomes. For a deeper dive into how triple therapy can optimize outcomes, consider reviewing recent discussions on triple therapy. While triple therapy offers clear benefits, the primary concern with the addition of an inhaled corticosteroid is the increased risk of pneumonia. Other potential side effects include oral candidiasis and dysphonia, which can often be mitigated with proper inhaler technique, while long-term use of high-dose corticosteroids can be associated with systemic effects such as osteoporosis and cataracts.

For patients where corticosteroid risks outweigh the benefits, alternative mechanisms are entering clinical practice. A pooled analysis of the phase 3 ENHANCE-1 and ENHANCE-2 trials evaluated ensifentrine, a first-in-class selective dual inhibitor of phosphodiesterase 3 and 4.² The trials included 975 patients receiving 3 mg twice-daily nebulized ensifentrine over 24 weeks, compared to 574 receiving placebo.² Ensifentrine reduced the rate of moderate to severe exacerbations with a rate ratio of 0.59 and delayed the transition from an infrequent exacerbator in GOLD group B to a frequent exacerbator in GOLD group E.²

A 24-week trial in a progressive disease treated for decades cannot establish long-term safety, and with only 18% of the trial population on concomitant inhaled corticosteroids, the additive efficacy of ensifentrine on top of maximal triple therapy remains unclear. Clinicians must weigh the exacerbation reduction benefits of any regimen against potential side effects, especially in patients with a history of recurrent infections. The decision to initiate complex therapies should

always involve a careful discussion with the patient about these risks and benefits, ensuring informed consent. The Oxford Handbook of Respiratory Medicine provides a concise reference for managing such complex decisions.

When Dual Therapy Remains Appropriate

Dual bronchodilator therapy remains the definitive ceiling of treatment for patients who experience infrequent exacerbations and lack eosinophilic inflammation. Not every patient with COPD requires triple therapy. For those with minimal symptoms and no history of exacerbations, or those whose exacerbations are infrequent and mild, dual bronchodilator therapy may remain the most appropriate choice. The goal is to provide the least intensive effective therapy, minimizing side effects and treatment burden. The step-up approach is specifically for patients whose disease activity indicates that their current regimen is insufficient.

Identifying which patients can safely remain on dual therapy requires looking beyond just exacerbation counts. The systematic review of 76 studies highlighted that while exacerbation history dominates risk prediction, disease severity or bronchodilator reversibility was a significant risk factor in 39 studies, and the presence of comorbidities was a significant predictor in 34 studies.⁶ Patients with very low blood eosinophil counts, such as those below 100 cells/ μ L, who experience an exacerbation may not derive significant additional benefit from an inhaled corticosteroid.

Systematic reviews of observational data do not prove that treating associated comorbidities will directly prevent COPD exacerbations, only that the conditions frequently coexist and compound clinical risk. In cases where patients have low eosinophils, clinicians might explore other avenues for exacerbation prevention, such as optimizing non-pharmacological interventions, addressing these comorbidities, or ensuring impeccable inhaler technique. Understanding the dual role of IL-33 in COPD inflammation can further inform these decisions.

While the evidence for stepping up to single-inhaler triple therapy after 1 moderate exacerbation is compelling for specific patient profiles, the long-term impact on overall mortality and the optimal duration of triple therapy remain areas of ongoing investigation. Whether an initial period of triple therapy can be safely de-escalated back to dual therapy in patients who achieve sustained exacerbation-free periods is a question that warrants further research. The focus remains on preventing future events, but the pathway to achieve that differs based on individual patient characteristics.

CLINICAL IMPLICATIONS

The shift in clinical thinking regarding COPD exacerbations is clear: one moderate event on dual bronchodilator therapy is no longer merely an inconvenience, but a critical inflection point. GPs and specialists must now view this as a prompt to re-evaluate, rather than simply treating the acute episode and returning to the status quo. The evidence points towards a more proactive approach, particularly when eosinophil counts suggest an ICS-responsive phenotype.

This means a more rigorous assessment of exacerbation history and blood eosinophil levels should become standard practice for patients on LAMA/LABA who experience a breakthrough event. Waiting for a second or third exacerbation before intensifying therapy risks further lung function decline and increased morbidity. The convenience of a single-inhaler triple therapy should also factor into adherence considerations, simplifying complex regimens for patients.

But the increased risk of pneumonia with ICS cannot be ignored. Clinicians must carefully balance the benefits of exacerbation reduction against this known side effect, especially in vulnerable populations. This isn't a

blanket recommendation for all, but a targeted strategy for those most likely to benefit, underscoring the need for personalized medicine in COPD management.

Pharmaceutical companies developing these SITTs have a responsibility to provide clear guidance on patient selection and risk mitigation, moving beyond broad marketing claims. The real-world effectiveness hinges on appropriate patient identification and careful monitoring, ensuring that the right patients receive this intensified therapy while minimizing adverse events.

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