

New Trends in Maintenance Therapy for Chronic Obstructive Pulmonary Disease (LABA/LAMA)

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While oxygen supplementation therapy was found to play a role in the management of chronic obstructive pulmonary disease (COPD), symptomatic treatment remains essential. Management options for COPD symptoms can be classified into three main categories: “rescue management for acute episodes of dyspnea”, “maintenance therapy”, and “treatment of acute COPD exacerbations”. Maintenance therapy is crucial in lowering the rate of acute COPD exacerbations in the future.



Background

Long-acting bronchodilators (**LABA**) and long-acting muscarinic antagonists (LAMA) are the mainstay treatment options for maintenance therapy in **COPD**. They were found to provide adequate symptomatic relief in COPD. **The traditional approach has always been a combination therapy of LABA plus an inhaled corticosteroid.**

LABA combinations with inhaled corticosteroids are usually reserved for patients with severe to very severe COPD; therefore, further studies were needed to define the first-line therapy for the symptomatic management of COPD in moderate COPD.

The use of an inhaled **corticosteroid** in the management of COPD can be considered as a two-edged sword. **Corticosteroids** are potent immunomodulators that are known to decrease bronchial wall edema and inflammation; both are common features of the pathogenesis of COPD.

On the other hand, corticosteroids are known to alter the immune response against different pathogens; therefore, the **risk of pneumonia seems to be higher** in patients receiving a LABA plus an inhaled corticosteroid when compared to those not receiving an inhaled corticosteroid.

However, the addition of an inhaled corticosteroid has also been reported to have a significant reduction effect on the risk of acute COPD exacerbations.

LABAs are **beta2 agonists**. They induce **smooth muscle relaxation** which results in bronchodilation. On the other hand, LAMAs mechanism of action is quite different. LAMAs block **acetylcholine-mediated** bronchoconstriction of smooth muscle cells. Because of the differences in the mechanisms of action, it has been hypothesized that LAMAs and LABAs might have a synergistic effect if combined.

To understand the best approach for the management of COPD symptoms in patients with moderate to very severe disease, one should understand how outcome measures are measured.

Research has focused on the following parameters while studying the **different treatment approaches**:

- Lung function
- Symptomatic scores
- Exacerbation rate.

Another important clinical factor to consider is the safety profile of the administered treatment.

Comparison Between the Different Treatment Options' Effects on Lung Function

Two important lung function parameters were studied while comparing the different treatment options for COPD. These are a trough forced expiratory volume in one second and peak forced expiratory volume in one second (trough and peak FEV1).

In summary, trough FEV1 and peak FEV1 at 12 weeks, 24 weeks and 52 weeks were **extremely significantly improved in patients receiving LABA/LAMA combination** compared to those receiving LAMA monotherapy or LABA/inhaled corticosteroid therapy. The difference in peak FEV1 between the different groups was both clinically and statistically significant; therefore, LABA/LAMA combinations were a clear winner in this regard. The p-value of the difference in mean between the different groups was less than 0.0001, an indicator of extreme statistical significance.

The LABA/LAMA combinations included: "indacaterol/glycopyrronium", "vilanterol/umeclidinium", "formoterol/aclidinium", and "olodaterol/tiotropium". All LABA/LAMA combinations showed similar efficacy.

Comparison Between the Different Treatment Options' Effects on Dyspnea and Rescue Medication

All patients with COPD should be prescribed a short-acting **bronchodilator** in addition to long-acting therapy as a rescue medication. These patients can develop dyspnea at any moment and rescue medication is usually needed; therefore, optimum maintenance therapy should lower the rate of use of rescue medication.

Dyspnea can be assessed by the international score known as **TDI** for a more objective evaluation of the COPD patient. In summary, LABA/LAMA combination therapy was found to be extremely superior to LAMA monotherapy alone or LABA/inhaled corticosteroid therapy. The general well-being of COPD patients receiving a LABA/LAMA combination was also superior when compared to those receiving LAMA alone or LABA/inhaled corticosteroid.

The rate use of rescue medication in patients receiving a LABA/LAMA combination was also significantly reduced compared to those receiving LABA plus inhaled corticosteroid therapy or LAMA alone.

Therefore, it was concluded that a LABA/LAMA combination as **first-line therapy for COPD patients is far more superior** compared to any other maintenance therapy option in the symptomatic control of the patient.

Comparison Between the Different Treatment Options Effects on COPD Exacerbations

LABA/LAMA combination therapy clearly **reduced the risk of hospitalization and acute COPD exacerbations** more than what was observed in the group of patients who received LABA plus an inhaled corticosteroid. The largest effect of LABA/LAMA combination was observed in the reduction of severe exacerbations; however, the **trend was still found in mild and moderate exacerbations**.

The Safety Profile of the Different Treatment Options

To understand the **safety profile of any drug**, one should take into consideration the following parameters:

- Rate of adverse effects
- Severe adverse effects
- Rate of drug discontinuation due to adverse effects
- Rate of drug discontinuation due to lack of efficacy
- Mortality rate

The rates of adverse effects or severe adverse effects of LABA/LAMA combination, LAMA monotherapy, or LABA/inhaled corticosteroid therapy were not different. **Pneumonia was found to be more commonly reported** in the group of patients receiving LABA/inhaled corticosteroid therapy compared to those receiving LABA/LAMA or LAMA alone. LABA/LAMA versus LAMA alone had a similar rate of pneumonia.

Cardiovascular disorders had a similar incidence in all groups. Death rates were also not different among the different treatment groups.

Another point that was in favor of LABA/LAMA combination therapy, when compared to LABA/inhaled corticosteroid therapy, is the **rate of discontinuation due to adverse effects**. Patients receiving a LABA/LAMA combination are less likely to undergo withdrawal of the combination because of side effects. On the other hand, patients receiving LAMA alone were **more likely to be switched to the LABA/LAMA regimen** because of the lack of efficacy of LAMA monotherapy.

Therefore, it is quite clear that LABA/LAMA combination therapy is not associated with a significantly higher risk of adverse effects when compared to other treatment options. Additionally, a LABA/LAMA combination is less likely to be associated with pneumonia when compared to a regimen that includes an inhaled corticosteroid.

Current Recommendation for Symptomatic Maintenance Therapy for COPD

Current evidence suggests that **LABA/LAMA combinations are clearly more effective** in the symptomatic management of COPD and are at least as safe as LAMA alone or LABA plus an inhaled corticosteroid regimen. Therefore, it is currently recommended to prescribe a LABA/LAMA combination as first-line therapy for any new patient diagnosed with stable moderate to severe COPD.

Patients who are currently on LABA plus inhaled corticosteroid therapy **should not be switched to LABA/LAMA if they show a good response** to the previous regimen. On the other hand, it might be a good idea to use a LABA/LAMA combination in patients already receiving a LAMA monotherapy because of the clearly added benefits.

References

Rodrigo GJ, Price D, Anzueto A, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease*. 2017;12:907-922. doi:10.2147/COPD.S130482.

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