



## THE VALUE OF LONG-ACTING MUSCARINIC ANTAGONIST (LAMA) PLUS LONG-ACTING BETA-AGONIST (LABA) IN TREATMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): A REVIEW STUDY

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### ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterised by chronic and progressive breathlessness, cough, sputum production, and airflow obstruction which is a major cause of morbidity and mortality whose prevalence is rising worldwide. Bronchodilators remain the main mode of COPD treatment, especially inhaled Beta2-adrenergic receptor agonists and inhaled anticholinergics. Long-acting bronchodilators remain more effective and convenient than short-acting bronchodilators for maintenance treatment in patients with moderate to very severe COPD. The combination of beta2-adrenergic receptor agonists and anticholinergics has been shown to provide superior bronchodilatory effect and act synergistically than either agent alone, possibly because of the different mechanisms of action at different parts of bronchus. The current treatment guidelines recommend the use of more long-acting bronchodilators for patients with moderate to severe stable COPD who remain symptomatic and with high exacerbation with single-agent bronchodilator therapy. The objective of this article is to review clinical data on combined bronchodilator therapy with beta2-adrenergic receptor agonists and anticholinergics in patients with COPD.

**Keywords:** Chronic obstructive pulmonary disease, Beta2-adrenergic receptor agonists, anticholinergics, bronchodilators

## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease characterised by chronic and progressive breathlessness, cough, sputum production, and airflow obstruction, which leads to morbidity and mortality of life, that need additional therapy for betterment of life ie.to decrease morbidity[1, 2]. Exacerbations are triggered by respiratory tract infections and environmental factors such as air pollution, smoking yet in approximately one third of cases , the cause still unknown [3]. Apart from smoking cessation and non-pharmacological treatments such as long term oxygen therapy in hypoxic patients, no intervention has been shown to reduce mortality. Management of the disease is multi-faceted and includes reducing risk factors[4], pharmacological treatments, education [5] and pulmonary rehabilitation[6], a large part of the economic burden of COPD is attributed to the cost of managing exacerbations, particularly those resulting in use of acute care services or hospitalization [7]. Chronic obstructive pulmonary disease (COPD), a leading cause of morbidity and mortality, is characterized by persistent airflow limitation that is usually progressive [8].

### Description of the intervention:

Management consist of three classes of inhaler device medications: long-acting beta-agonists (LABA), long-acting muscarinic agonists (LAMA), and inhaled corticosteroids (ICS)[9]. Bronchodilators are recommended as first-line therapy in symptomatic patients with airflow limitation, and are fundamental to the management of stable COPD [10, 11]. If the disease cannot be controlled adequately with LAMA or LABA monotherapy, administration of two or more medications from different classes may prove beneficial. When two classes of medications are required, LAMA plus LABA (LAMA+LABA) and LABA plus ICS (LABA+ICS) are often selected because these combinations can be administered via one medication device [12-14], which is most beneficial for improving patient adherence [15]. However, treatment options are chosen primarily based on exacerbation history and symptom assessment (Table 1)

**Table 1. Combined Assessment of COPD**

Patient	Characteristic	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk Less Symptoms	GOLD 1-2	$\leq 1$	$< 10$	0-1
B	Low Risk More Symptoms	GOLD 1-2	$\leq 1$	$\geq 10$	$\geq 2$
C	High Risk Less Symptoms	GOLD 3-4	$\geq 2$	$< 10$	0-1
D	High Risk More Symptoms	GOLD 3-4	$\geq 2$	$\geq 10$	$\geq 2$

**Abbreviations:** COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic

Obstructive Lung Disease; mMRC, Modified Medical Research Council; CAT, COPD Assessment Test

Long-acting muscarinic antagonist (LAMA) and long-acting b<sub>2</sub>-agonist (LABA) combination therapy is recommended if symptoms persist despite treatment with bronchodilator monotherapy [11]. Fixed-dose combinations (FDCs) of LAMA + LABA can maximize the bronchodilator response without increasing the dose of individual components by LABA-mediated stimulation of b<sub>2</sub>-adrenergic receptors, LAMA-mediated inhibition of acetylcholine action at muscarinic receptors, and signaling cross-talk-induced synergistic bronchodilation effects [16, 17]. Further, the safety of LAMA + LABA combination therapies and monotherapies is comparable [18, 19]

LAMA + LABA Fixed-dose combinations is approved for use in many countries which shows that treatment with LAMA + LABA significantly improved lung function[9, 20, 21], quality of life [20, 22], and transition dyspnea index [22] compared with either monotherapy in patients with moderate-to-very severe COPD [Global Initiative for Chronic Obstructive Lung Disease[23]

### **LAMA (Long-acting muscarinic antagonist):**

The distribution of muscarinic receptors throughout the bronchial tree is mainly restricted to muscarinic M<sub>1</sub>, M<sub>2</sub> and M<sub>3</sub> receptors [24, 25]. Muscarinic M<sub>1</sub> receptors are expressed by epithelial cells, where they play a modulatory role in electrolyte and water secretion, and in the ganglia, where they facilitate parasympathetic neurotransmission [26, 27]. Muscarinic M<sub>2</sub> receptors are expressed by neurons, where they function as autoreceptors, inhibiting the release of acetylcholine from both preganglionic nerves and from parasympathetic nerve terminals. In response to acetylcholine, goblet cells also produce mucus [28]. Muscarinic M<sub>2</sub> autoreceptors are dysfunctional in allergic asthma due to eosinophil-derived release of major basic protein, which acts as an allosteric antagonist of the M<sub>2</sub> receptor [29], augmenting acetylcholine release. M<sub>2</sub> receptors are widely expressed by airway mesenchymal cells such as fibroblasts and smooth muscle cells [24]. Which are probably the best characterized subtype and are the dominant receptor subtype in the regulation of mucus secretion from submucosal glands and airway smooth muscle contraction[24]. As a result, muscarinic M<sub>3</sub> receptors are the primary target for LAMAs .LAMAs dilate the airway by selectively blocking acetylcholine M<sub>3</sub> receptors [30] and by inhibiting bronchoconstriction. LAMAs confer anti-inflammatory, anti-airway remodelling effects [31].

LAMAs bind to human M<sub>1</sub>–M<sub>5</sub> receptors in a concentration-dependent manner and have higher selectivity for M<sub>3</sub> receptors than for M<sub>2</sub> receptors, and dissociate more slowly from the M<sub>3</sub> receptors than they do from the M<sub>2</sub> receptors [32, 33]. The association of LAMA with the M<sub>3</sub> receptor is assumed for faster onset of action.

## **Clinical efficacy of LAMAs in chronic airway diseases:**

In COPD, The Understanding Potential Long-term Impacts on Function with LAMA (UPLIFT) study [34] demonstrated that when LAMA used the mean values for FEV1 and forced vital capacity (FVC) before and after bronchodilation showed significant improvement. LAMA also decreased dyspnea, exacerbation and increased quality of life.

## **Safety Considerations:**

LAMA/LABA combination products have precautions for worsening of narrow-angle glaucoma and urinary retention as a result of administration of a muscarinic antagonist. However, the incidence of these effects are low and not observed in clinical trials. An increased incidence of morbidity and mortality from cardiovascular causes was initially a concern with LAMA, but the available evidence does not indicate an increased incidence of cardiovascular outcomes in patients without significant cardiac comorbidities [35]. Increased cardiovascular risk is also a precaution with these medications because of the LABA component; however, there are inconsistent data regarding this warning [36].

The use of LAMA/LABA combination agents have common adverse events in clinical trials that are cough and nasopharyngitis. These findings are confirmed in the different studies [37-41].

## **LABA (long-acting b2-agonist):**

The principal action of beta2-agonists is to relax airway smooth muscle by stimulating beta2-adrenergic receptors. Which increases the intracellular messenger cyclic AMP responsible for the control of smooth muscle tone [42]. Thus, activation of the beta2-adrenergic receptor results directly in bronchodilation. Inhaled beta2-agonists also activate beta2-receptors in the smooth muscle of the airway leading to a cascade of reactions resulting in bronchodilation. It also acts through other mechanisms such as respiratory muscle function or mucociliary clearance. Beta2-agonists are particularly useful bronchodilators because they reverse bronchoconstriction regardless of the initial cause. The commonly used long-acting beta2-agonists, salmeterol and formoterol, both have a higher selectivity for beta2-receptors than beta1-receptors. Beta2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-receptors are the predominant receptors in the heart, although 10% to 50% of the total beta receptors in the heart are comprised of beta2-receptors [43]. The presence of beta2-receptors in the heart raises the possibility that even highly selective beta2-agonists may have cardiac effects. The mechanism for activating beta2-receptors differs between formoterol and salmeterol. Formoterol is taken up into a membrane depot from where it gradually leaks out to interact with the receptor, while salmeterol binds near the receptor, allowing it to remain at the receptor site, continually binding and releasing [44]. In both cases stimulation of the beta2-receptors leads to changes in intracellular Ca<sup>2+</sup> homeostasis and bronchodilation [45]. The duration

of action for long-acting beta2-agonists is approximately 12 hours, and therefore LABAs are usually taken twice daily.  $\beta$ 2-adrenergic receptor agonists bind to adrenoreceptors on the surface of smooth muscle cells at all airway levels, even in the small airways involved in COPD, leading directly to smooth muscle relaxation and subsequent bronchodilation [46, 47].

### **Lung function:**

Formoterol and salmeterol have both demonstrated significant improvements in lung function [48-54]. Improvements in pre-bronchodilator forced expiratory volume in 1 second (FEV1) ranged from 50-90 mL compared with placebo [49, 52, 55-57]. Bronchodilation was rapid in onset with formoterol [58], although salmeterol had an onset of action slower than salbutamol or ipratropium bromide [59]. Further, in a post-hoc analysis from the 3-year Towards a Revolution in COPD Health (TORCH) study, salmeterol reduced the rate of decline in lung function by 13 mL/year.

### **Side effect:**

Possible side effects of LABAs include cardiac effects such as arrhythmia and palpitations, muscle tremors, headache and dry mouth [60].

### **Combination Therapy with LABAs and Long-Acting Inhaled Anticholinergics:**

Both tiotropium and long-acting beta2-agonists are recommended for treatment of stable COPD.  $\beta$ 2agonists can amplify muscarinic antagonist-mediated smooth muscle relaxation by modulating cholinergic neurotransmission and decreasing acetylcholine release, and muscarinic antagonists can augment  $\beta$ 2-agonist-mediated bronchodilation by reducing the bronchoconstrictor effects of acetylcholine [16]. The complimentary mechanisms of action of LABAs and LAMAs elicit additive effects on lung function, and provide a rationale for combining the two agents to optimize bronchodilation. Mechanisms that most likely involve reduced airway resistance, improved inspiratory capacity and reduced hyperinflation may confer benefits in terms of exacerbations [61]. Treatment with LABA/LAMA versus with single treatment was evident in the SPARK study [62] and the inclusion of data from ongoing studies such as DYNAGITO have clarified the role of LABA/LAMA versus single bronchodilator treatment in the prevention of COPD exacerbations, especially in high-risk populations. The incidence of pneumonia have seen significantly lower in the LABA/LAMA group versus the LABA/ICS-treated patients. Numerous randomized, double-blind, placebo-controlled, phase III studies (with durations of 6, 12, and 52 weeks), including parallel-group and crossover studies, have shown that treatment with LAMA / LABA significantly improved lung function [9, 20, 21] quality of life [20, 22] and transition dyspnea index [22] compared with either monotherapy in patients with moderate-to-very severe COPD [Global Initiative for Chronic Obstructive Lung Disease (GOLD), grades 2-4] in the Japanese subpopulation of replicated phase III studies (TONADO 1 and 2) LAMA/LABA was

superior to either monotherapy for lung function and St George's Respiratory Questionnaire (SGRQ) total score at 24 weeks, being consistent with results of the overall population [14]. SPARK study was a clinical trial of LABA/LAMA combination (also known as QVA149).[62, 63] Clinical trials of the fixed dose LABA/LAMAs have reported similar or lower frequencies of exacerbations compared to the monotherapy arms.[62, 64-67] In the ILLUMINATE study, indacaterol/glycopyrronium was associated with significantly better lung function, as measured by FEV1, across the entire duration of the study; however, symptom scores were not significantly different.[68] The efficacy of combination therapy with LAMA and LABA has also been compared with monotherapy with either agent in a randomized, double-blind, 3-way, crossover clinical trial conducted by van Noord and coworker[69]. Seventy-one patients with moderate-to-severe COPD received a combination of both agents administered QD for three 6week periods. Combination therapy resulted in significantly higher peak and trough FEV1 and FVC values compared with monotherapy with either agent. Patients receiving combination treatment also experienced greater improvements in both daytime (0–12 h) and nighttime (12–24 h) FEV1 and FVC than patients receiving either drug alone. Daytime use of rescue medication was significantly lower in the LAMA and LABA combined than in patients receiving monotherapy; however, there were no significant differences between groups with respect to nighttime rescue medication use. when both LAMA and LABA have additive effect in bronchodilation of bronchus which reduce exaggeration , air entry and improve life quality. LAMA+LABA therapies were associated with significantly better results for exacerbation rates, trough FEV1, pneumonia, and SGRQ total score change more than minimal clinically important difference

## CONCLUSION

The treatment of chronic obstructive pulmonary disease (COPD), long-acting muscarinic antagonists plus long-acting beta-agonists (LAMA+LABA) are associated with fewer exacerbations, larger improvement of forced expiratory volume in one second (FEV1), reduced risk of pneumonia, and more frequent St. George's Respiratory Questionnaire (SGRQ) total score improvement exceeding the minimal clinically important difference (4 points or greater). These data were supported by low or moderate quality of evidence generated from mainly people with moderate to severe COPD in heterogeneous trials with observation period less than one year. The findings of the review support the recently updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance, which favours LAMA+LABA overlong-acting beta-agonists plus inhaled corticosteroids (LABA+ICS) in B,C and D group.

### Conflict of interest:

None

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