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# EFFICACY OF DOUBLE BRONCHODILATOR THERAPY FOR MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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**ABSTRACT:**

***Background:*** *Chronic obstructive pulmonary disease (COPD) represents a significant cause of global morbidity and mortality, with a substantial economic impact. Long-acting bronchodilators are the mainstay of therapy due to their proven efficacy. The Global initiative for chronic Obstructive Lung Disease (GOLD) recently recommended combining long-acting bronchodilators with differing mechanisms of action for greater efficacy but supportive evidence is limited at present.* ***Objective:*** *To assess the efficacy of double bronchodilator therapy, i.e. long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs), for management of chronic obstructive pulmonary disease.* ***Methods:*** *This longitudinal study was carried out at the Dept. of Chest Medicine at Liaquat University of Medical & Health Sciences, Jamshoro from November 2017 to July 2018 on a sample of 377 pre-diagnosed patients of COPD, aged 18 to 48 years (chosen via non-probability, consecutive sampling) presenting to the chest medicine outpatient department. After taking written informed consent from subjects, data was collected using a pre-structured, interview based questionnaire containing inquiries about basic sociodemographic information and detailed disease particulars at the time of presentation and disease condition upon follow-up after 4 weeks of double bronchodilator therapy. The data obtained was analyzed using MS. Excel 360 and SPSS v. 21.0.*

***Result:***

*A total of 377 subjects were enrolled during the study duration. The mean age of sample stood at 47 years (SD ±7.5) and most of the subjects (71.35%) were males. The subjects reported a significantly lower incidence of disease exacerbation, need for oxygen administration and hospitalization. The self-rated symptom score was also encouraging. No adverse effects were reported by the patients during the study period.*

***Conclusion:*** *After carefully considering the results, it can be concluded that double bronchodilator therapy is significantly more efficacious than single bronchodilator therapy of either LAMA or LABA.*

***Keywords:*** *Long-Acting Muscarinic Antagonists (LAMAs), Long-Acting β2-Agonists (LABAs), Bronchodilator Therapy, Double Bronchodilator Therapy, Chest Medicine, and Chronic Obstructive Pulmonary Disease.*

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## INTRODUCTION:

Currently the fourth leading cause of death globally, chronic obstructive pulmonary disease (COPD) has overall prevalence in adults aged >40 years estimated currently at 9–10%. **[1]** The World Health Organization (WHO) estimates that, by 2020, COPD will be the third leading cause of mortality and the fifth leading cause of morbidity in the world. **[2]**

The primary cause of COPD is smoking, with 30–40% of smokers estimated to develop the disease. COPD is characterized by poorly reversible airflow obstruction and a chronic inflammatory response in the lungs. The pathological hallmark features of COPD are airway inflammation associated with small airway narrowing, mucus hypersecretion and parenchymal destruction. **[3]**

Bronchodilators are the primary pharmacological intervention for COPD. These drugs improve symptoms and quality of life by improving airflow and hence gaseous exchange, and by reversing air trapping and dynamic lung hyperinflation through dilatation of the distal airways. **[4]** Long acting bronchodilators with up to 24 h bronchodilator activity are used as maintenance therapy for the prevention and reduction of symptoms. **[5]**

There are two classes of long acting bronchodilators that act by different mechanisms, long acting muscarinic antagonists (LAMAs) and β2-adrenoceptor agonists (LABAs). LAMAs inhibit the action of acetylcholine at muscarinic receptors, while LABAs enhance cAMP signaling through stimulation of β2-adrenergic receptors. **[6]**

Long-acting inhaled bronchodilators relieve symptoms more effectively than short-acting bronchodilators and are central to the management of patients with chronic obstructive pulmonary disease. **[7]** However, symptoms of patients with COPD are often inadequately controlled by long-acting bronchodilator monotherapy. Hence, current guidelines/strategy recommend that combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared with increasing the dose of a single bronchodilator. **[8]**

The Global initiative for chronic Obstructive Lung Disease (GOLD) recently suggested that combining long-acting bronchodilators with differing mechanisms of action may improve efficacy of pharmacologic therapy but supportive evidence is limited at present. **[9]** To assess the efficacy of double bronchodilator therapy, i.e. long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs), for management of chronic obstructive pulmonary disease.

## METHODOLOGY:

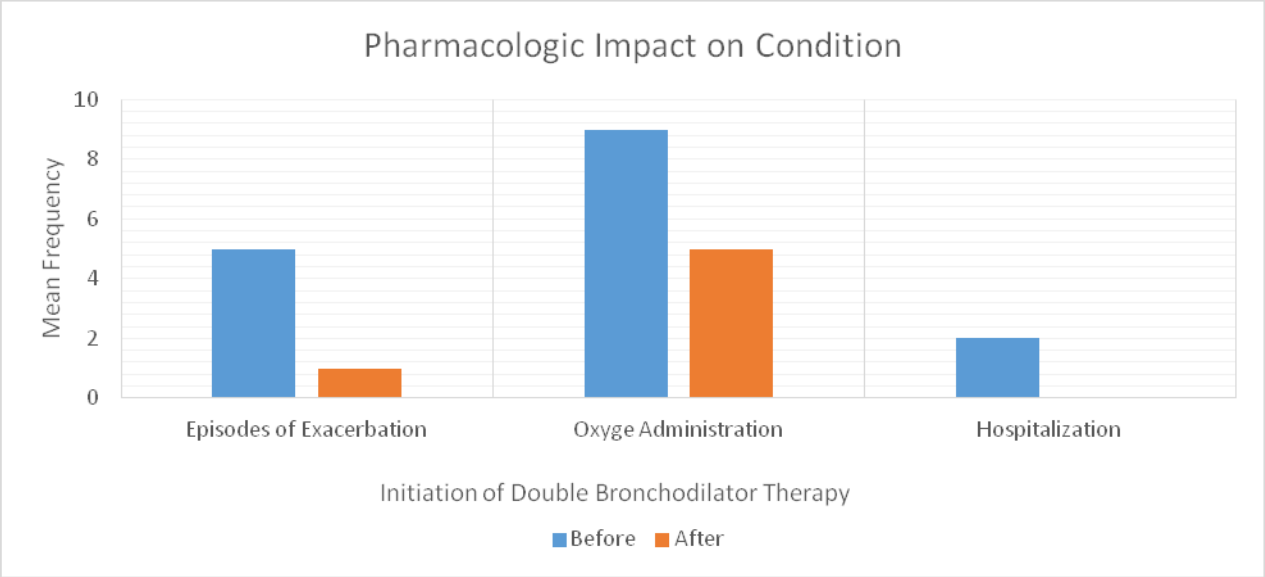
This longitudinal study was carried out at the Dept. of Chest Medicine at Liaquat University of Medical & Health Sciences, Jamshoro from November 2017 to July 2018 on a sample of 377 pre-diagnosed patients of COPD, aged 18 years and above (chosen via non-probability, consecutive sampling) presenting to the chest medicine outpatient department.

After taking written informed consent from subjects, data was collected using a pre-structured, interview based questionnaire containing inquiries about basic sociodemographic information and detailed disease particulars at the time of presentation and disease condition upon follow-up after 4 weeks of double bronchodilator therapy. Patients were required to record a total daily symptom score (obtained by self-evaluating the morning and evening symptoms, ie, cough, wheezing, sputum production and shortness of breath).

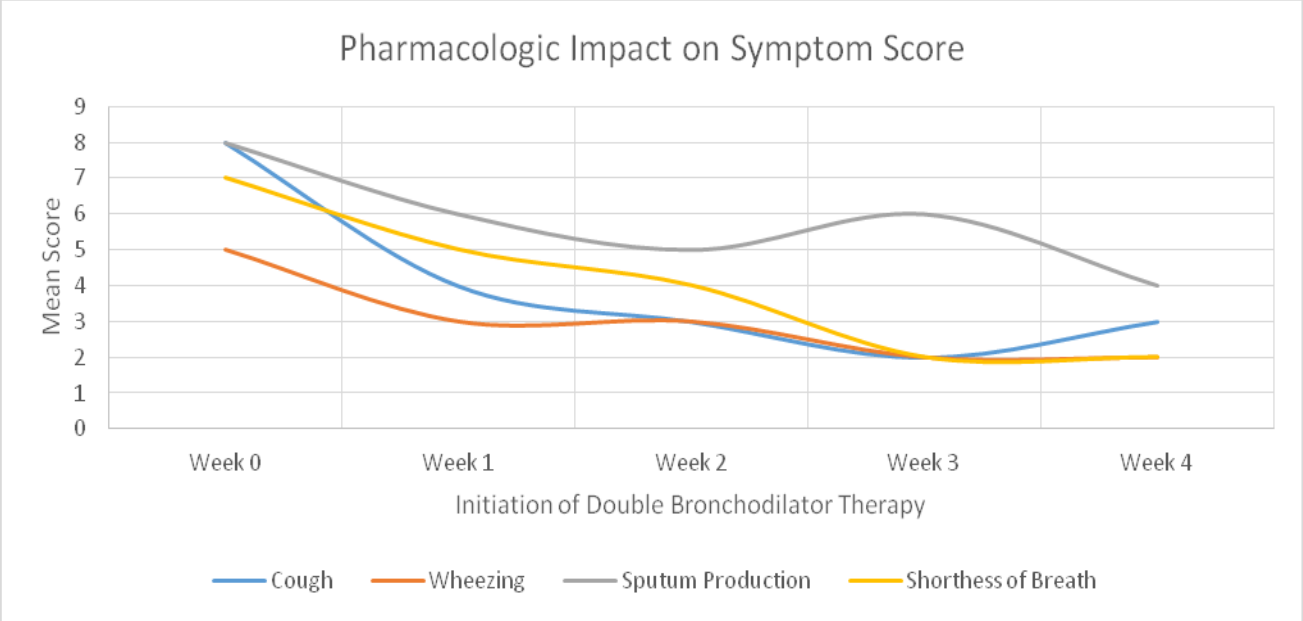
Patients with concomitant respiratory tract infection 4 weeks before or during screening, history of asthma and/or a clinically significant electrocardiogram (ECG) abnormality were excluded from the sample. The data obtained was analyzed using MS. Excel 360 and SPSS v. 21.0.

## RESULTS:

A total of 377 subjects were enrolled during the study duration. The mean age of sample stood at 47 years (SD ±7.5) and most of the subjects (71.35%) were males. The subjects reported a significantly lower incidence of disease exacerbation, need for oxygen administration and hospitalization.




The self-rated symptom score was also encouraging.




No adverse effects were reported by the patients during the study period.

## DISCUSSION:

The bronchodilator effects of β2-adrenoceptor agonists and anti-muscarinics used alone in laboratory models demonstrate a linear response at low concentrations followed by a flatter curve at higher concentrations. Inhaled delivery in humans also shows a similar dose–response curve, with a reduced effect at higher doses. In clinical practice, this means that higher doses may achieve extra benefit but along comes a risk of adverse effects through systemic absorption. **[10]** However, none of our study subjects reported adverse effects.

Clinical development programmes in COPD patients have defined the doses of long acting bronchodilator monotherapies (either LABAs or LAMAs alone) with the optimum therapeutic index, and discovered differences between drugs in terms of onset of action and dose responsiveness, e.g. formoterol is an example of a β-adrenoceptor agonist with a fast onset of action and a relatively linear dose-response curve. **[11]**

Additional bronchodilation can be achieved by

combining LABAs and LAMAs due to the distinct and complementary mechanisms of action. This concept is well accepted for the short acting β2-adrenoceptor agonist and anti-muscarinic combination inhaler containing ipratropium bromide/albuterol. **[12]**

Studies combining long acting bronchodilators administered using separate devices have also demonstrated an additive benefit. The magnitude of lung function additive benefit achieved has varied greatly between studies, due to differences in the timing of lung function, the lack of placebo control in some studies and relatively small sample sizes. Nevertheless, these studies support the clinical rationale for dual long acting bronchodilator therapy. Furthermore, it has been demonstrated that increasing the dose of the LABA, indacaterol, from 300 to 600 μg day–1 was less effective than using indacaterol 300 μg with the LAMA, glycopyrronium, delivered in the same inhaler. **[13]**

The patterns of response to a single bronchodilator monotherapy can vary between patients. Some patients may show much greater responsiveness to one class of bronchodilator compared with the other. Furthermore, it is well known that the magnitude of bronchodilation with the same drug can vary from day to day. Combination treatment with a LABA plus a LAMA has the potential to maximize bronchodilation and so overcome such variations in response that occur with monotherapy. **[14]**

Laboratory studies suggest that synergistic effects may occur between LABAs and LAMAs by a variety of mechanisms. For example, β2-adrenoceptor agonists can activate pre-junctional β2-adrenoceptors to reduce acetylcholine release, and inhibitory crosstalk may exist between M3 receptors and β2-adrenoceptors in airway smooth muscle. **[15]**

It could be hypothesized that the use of LAMA/LABA will enhance the possibility of synergistic interactions by co-deposition of LABAs and LAMAs in the airways. This study reiterates the hypothesis and paves way for large scale clinical trials to take this information ahead and propose fresh guidelines for patient benefit.

## CONCLUSION:

After carefully considering the results, it can be concluded that double bronchodilator therapy is significantly more efficacious than single bronchodilator therapy of either LAMA or LABA with no reported added adverse effects.

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