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EFFECT OF DUAL AND TRIPLE DRUG THERAPY IN COPD MANEGEMENT

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ABSTRACT

Today, chronic obstructive pulmonary disease is the third leading cause of death globally. Over the past ten years, the number of pharmaceutical medications available to treat COPD patients has increased. Patients with advanced COPD are especially vulnerable to negative outcomes and issues with medical treatment. According to guidelines, patients with moderate COPD should take a combination of bronchodilators, particularly muscarinic antagonist and B2-agonist, as well as B2-agonist and inhaled corticosteroid. Patients with severe COPD should take a combination of muscarinic antagonist, B2-agonist, and inhaled corticosteroid. Compared to either medication alone, they may exhibit additive and synergistic bronchodilation. To compare the course of the disease in patients undergoing dual bronchodilation with a LABA + LAMA as a fixed combination (dual bronchodilation) and those undergoing triple therapy of a LABA + LAMA & ICS, we have taken data for analysis in the current publication. We hypothesized that triple dosage therapy would be safer and more effective than dual bronchodilation.

KEYWORDS: Dual therapy, Triple therapy, COPD, Inhaled corticosteroids, LABA, LAMA.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder marked by increased airflow obstruction and symptoms including cough, sputum production, that representing a major global health concern due to its high morbidity and mortality rates.[1] COPD is characterized by persistent inflammation and structural alterations in the lungs and airways that restrict airflow and impede gas exchange. Its pathogenesis includes chronic obstructive bronchiolitis, which is defined by airway inflammation and fibrosis, and emphysema, which is characterized by lung parenchyma degradation and loss of elasticity.[2] Although smoking is the primary risk factor for most cases of COPD, the disease's development and course are also influenced by exposure to ambient tobacco smoke, pollution, occupational dust and chemicals, socioeconomic factors, and respiratory infections.[3] Chronic bronchitis and emphysema (damage to parenchymal tissue) are the two main conditions that worsen COPD. Chronic bronchitis: Prolonged exposure to allergens that harm the lungs and airways is typically the cause of chronic bronchitis. Many medical experts agree that smoking cigarettes is the primary cause of persistent bronchitis. Workplace conditions and air pollution may also have a role.[4] Emphysema: Emphysema develops progressively over time. It may result from: Extended and significant exposure to hazardous gases is the most frequent cause, which is still smoking cigarettes. Particulate matter and sulphur dioxide are additional environmental pollutants in addition to biomass fuels.[5] Currently, the Global Initiative for COPD (GOLD) promotes the "ABCD" assessment of COPD patients based on symptom severity (measured by questionnaire) and exacerbation risk (low risk, defined as no more than one moderate-severer exacerbation in the previous year). (1). Patients with mild symptom severity and little risk of aggravation are included in GOLD group A. (2). Patients with high symptom severity and minimal risk of exacerbation are included in GOLD group B. (3).Patients with modest symptom intensity but a high risk of exacerbation are included in GOLD group C. (4).According to the Global Initiative for Chronic Obstructive Lung Disease, patients in GOLD group D have severe symptoms and a high risk of exacerbation.[6] COPD is treated with dual therapy and triple medication inhaler therapy. However, overprescribing triple therapy can increase the risk of pneumonia and other adverse effects associated with inhaled corticosteroids (ICS).[7]

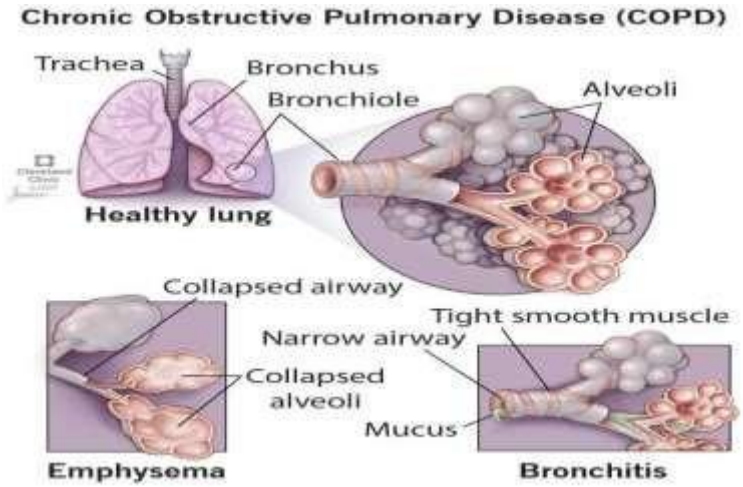

Figure 1: Chronic obstructive pulmonary disease.

The main objectives of COPD management are to reduce disease exacerbations, enhance lung function, and improve quality of life. The cornerstones of COPD treatment are inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), quitting smoking, pulmonary rehabilitation, and/or home oxygen therapy. Patients with COPD need to start these medicines right once because of their higher risk of developing new exacerbations, ongoing decline in lung function, poorer quality of life, and premature death. The first line of treatment for COPD is a LAMA or a LAMA/LABA dual inhaler, according to the Global Initiative for Obstructive Lung Disease (GOLD).[8] Global Strategy for COPD Diagnosis, Treatment, and Prevention, the Global Initiative for Chronic Obstructive Lung Disease [GOLD] Patients advise taking a combination of two drugs if they are in Groups A and B and have fewer symptoms but a low risk of exacerbations. Despite having fewer symptoms and a higher risk of exacerbations, Group C receives a fixed dosage of corticosteroids. Severe airway inflammation, two or more exacerbations, or hospitalization annually are characteristics of Group D.[9] The current study aimed to examine the effectiveness of triple-drug therapy vs dual-drug therapy in COPD patients with respect to improvements in lung function as assessed by exacerbation rates. With a focus on quality of life, lung function improvement, and exacerbation rates, this study evaluates the safety and effectiveness of triple therapy (LABA+ICS+LAMA) versus dual therapy (LABA+ICS) for the treatment of severe COPD. In terms of comorbidities, lung pathology, and the disease's natural progression, COPD is a complex illness that varies from person to person. Over the past forty years, researchers have established a number of theories or hypotheses on the beginning of COPD: The American hypothesis claimed that the development of emphysema is the main risk factor for the development of COPD, the Swedish hypothesis concentrated on genetic factors, the Dutch hypothesis highlighted the presence of increased airway responsiveness, and the British hypothesis asserted that the presence of cough and sputum was the key factor in COPD.[10, 11]

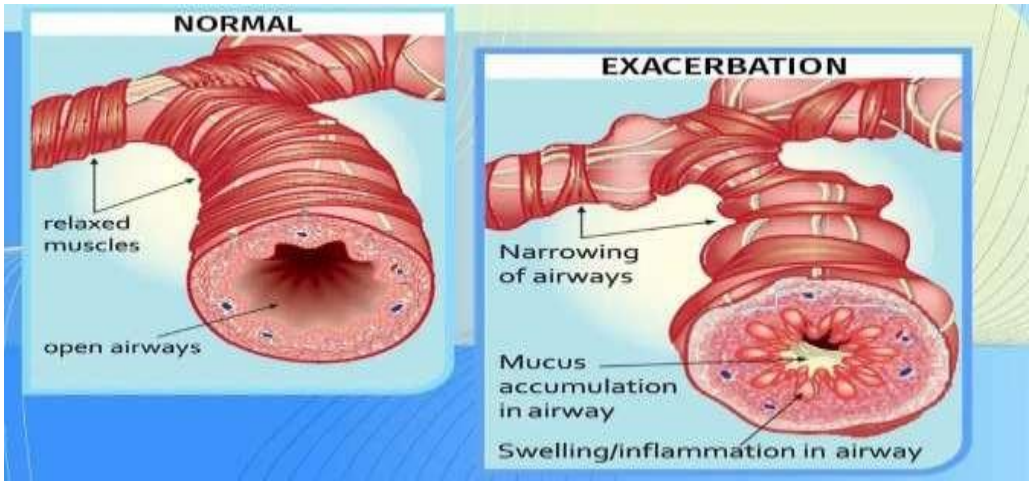

Figure 2: Exacerbation of COPD.

According to recent study, triple therapy which combines LABAs, LAMAs, and inhaled corticosteroids(ICS) may provide further advantages for some COPD patient subgroups, especially those with severe illness or

recurrent exacerbations. Triple therapy aims to improve lung function and reduce the risk of exacerbation by treating both inflammation and bronchodilation.[12]

BURDEN OF COPD

- Prevalence: Current estimates of COPD prevalence vary widely due to differences in survey methodology, diagnostic criteria, and analytical techniques. In all of these epidemiologic studies, spirometry was the sole technique employed to describe COPD. The lowest prevalence is found in estimates based on self-reporting a medical diagnosis of COPD or a related condition. For example, most national statistics show that less than 6% of persons have a COPD diagnosis.[13]
- Morbidity: Common markers of morbidity include hospital stays, ER visits, and doctor visits. Research to date indicates that the morbidity of COPD increases with age.
- Morbidity may also be impacted by concurrent chronic conditions (such as diabetes mellitus, musculoskeletal impairment, and cardiovascular disease) associated with smoking, aging, and/or COPD.[14]
- Mortality: The World Health Organization (WHO) publishes mortality data for particular causes of death for each of its regions annually. However, results should be interpreted with caution due to the variable usage of COPD nomenclature. In the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), deaths from COPD or chronic airway obstruction fall under the broad category of "COPD and allied conditions".[15]

PATHOBIOLOGY

- Inflammatory changes: The inflammation observed in the lungs of COPD patients appears to be a modification of the normal inflammatory response to chronic irritants such as cigarette smoke. Genetics may have a factor, even if the precise origins of this elevated inflammation are still unknown. COPD is characterized by an increase in macrophages in the lung parenchyma, pulmonary arteries, and peripheral airways in addition to an increase in active neutrophils and lymphocytes.[16]
- Structural changes: There is compelling evidence that COPD patients' lungs have an imbalance between anti-proteases that neutralize the action of proteases derived from inflammatory and epithelial cells that degrade connective tissue components. Inflammation may occur prior to the development of fibrosis, or the overproduction of muscle and fibrous tissue. The airway wall itself may develop tiny airways as a result, which could lead to obstruction.[17, 18]

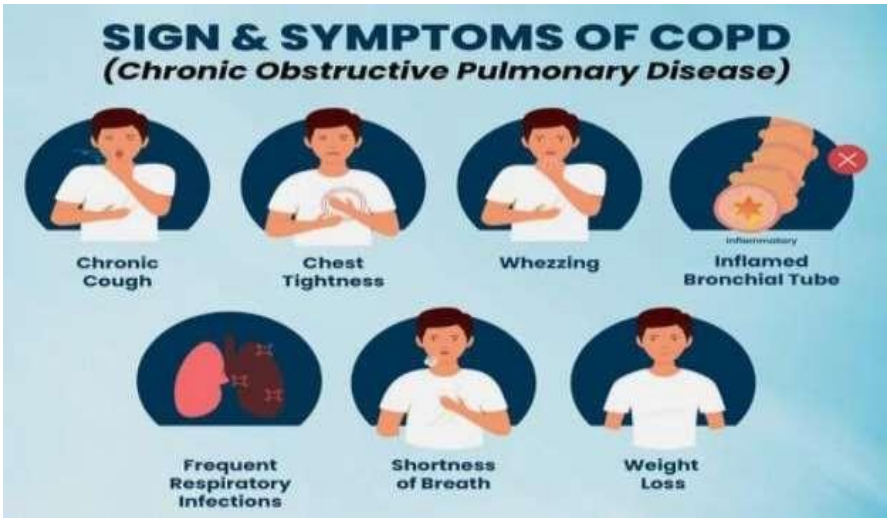

Figure 3: Symptoms of COPD.

PATHOPHYSIOLOGY

- Airflow obstruction and gas trapping: The combination of parenchymal degradation (emphysema, which reduces the lung parenchyma's natural elastic rebound) and small airways disease (which increases airway resistance), the relative contributions of which vary from person to person, causes airflow obstruction in COPD. . As a result, these changes lessen the airways' ability to remain open during expiration. Lack of small airways can also result in mucociliary dysfunction and airflow obstruction.[19, 20]
- Exacerbations: Exacerbations of respiratory symptoms in COPD patients can be caused by environmental pollutants, respiratory infections with bacteria or viruses (which may coexist), and unknown factors. This can result in increased systemic and airway inflammation, increased gas trapping.[21]

THE FACTORS INFLUENCING COPD PROGRESSION

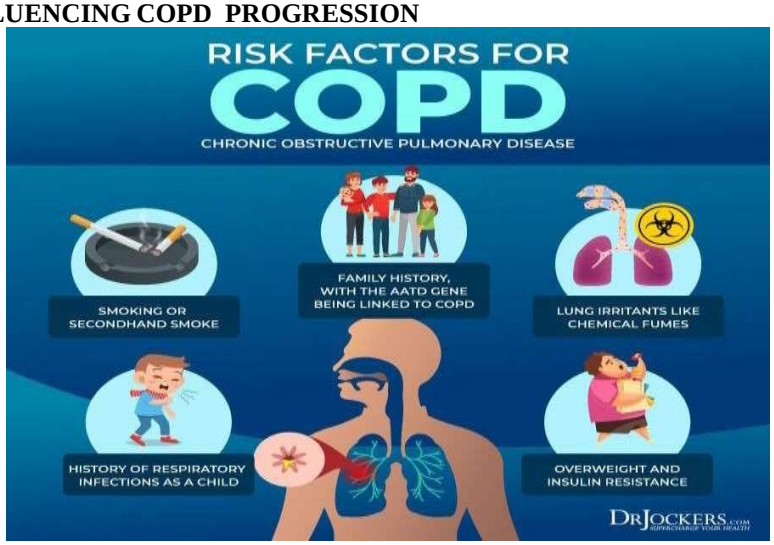

Figure 4: Risk factors of COPD.

- Genetic factors
- Age and gender
- Exposure to dust
- Asthma
- Smoking
- Socioeconomic and related factors
- Infections

CLASSIFICATION OF SEVERITY OF AIR LIMITATION {AS PER GOLD GUIDELINES}

STAGES	CHARACTERSTICS	COMMENTS
Mild COPD	• Chronic symptoms (cough, sputum production) • FEV1/FVC<70% • FEV1 80% predicted	Cough and sputum production proceeds along with airflow limitation by many years. At this stage, the patient may be unaware regarding their abnormal lung function.
Moderate COPD	• With or Without chronic symptoms (cough, sputum production) • FEV1/FVC<70% • 50% FEV1 80% predicted	Symptoms gradually progress at this stage, with uneasiness and shortness of breath typically developing on forceful effort.
Severe COPD	• With or Without chronic symptoms (cough, sputum production) • FEV1/FVC<70% • 30% ≤FEV1 < 50% predicted	Emphysema is typically seen at this stage which limits the physical activities and exacerbation develops at the beginning of this stage.
Very Severe COPD	• With or Without chronic symptoms (cough, sputum production) • FEV1 ≤ 30% predicted	Exacerbations may be life-threatening.[22, 23]

EFFECTIVENESS OF DUAL AND TRIPLE DRUG THERAPY IN COPD

(A). DUAL THERAPY: It is a type of combination therapy that uses two different drugs or treatments at the same time to treat one illness. The concurrent use of two distinct drugs or therapeutic approaches to treat a single medical disease is known as dual therapy.

COMMON DUAL DRUG COMBINATIONS FOR COPD.

- ❖ LAMA + LABA (Dual Bronchodilators): Umeclidinium. Vilanterol (Long-acting bronchodilators), Tiotropium, Olodaterol (Once-daily treatment), Glycopyrronium, Formoterol (Twice-daily), Indacaterol, Glycopyrronium (Twice-daily).
- ❖ ICS + LABA (Steroid/Bronchodilator): Budesonide, Formoterol (Often used for reducing exacerbations), Fluticasone, Salmeterol (Combination treatment), Fluticasone, Vilanterol (Combination treatment).
- ❖ SABA + SAMA (Short-acting): Albuterol, Ipratropium **(**For quick relief**).**

DUAL DRUG THERAPY: For a few years, physicians have begun combining drugs by prescribing various inhalers for advanced clinical efficacy. However, when we refer to the dual combination treatment with bronchodilators, we mean both drugs with a different mechanism of action and duration of action that lengthens the duration of bronchodilators with a lower

risk of side effects, as opposed to increasing the dosage of a single bronchodilator. Many combinations of LABA and LAMA inhalers are currently authorized for treatment in COPD.[24, 25] Dual combination therapy, on the other hand, usually combines two drugs with different mechanisms of action into a single inhaler. His COPD can now be treated with a variety of combination therapies that fit into three categories.[26]

- Combination of beta-agonist and muscarinic antagonist.
- Combination therapy using long acting beta agonists and inhaled corticosteroids.
- Bronchodilator with PDE-4 inhibitor.

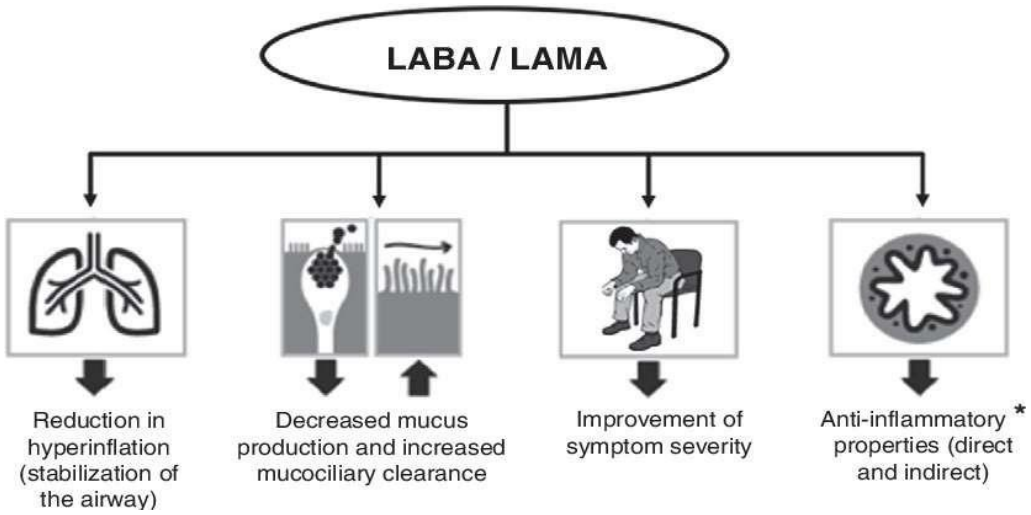

Figure 5: Moa Of Laba/Lama.

➢ COMBINATION OF BETA-AGONIST & MUSCARINIC ANTAGONIST: All combinations of long-acting inhaled beta-agonists and anti-muscarinics have improved lung function, but it has been challenging to demonstrate that these benefits lead to clinically significant outcomes like improvements in exercise capacity or shortness of breath. Combination therapy may help manage symptoms and prevent mild symptom exacerbations, according to some research.[27] Indacaterol-glycopyrronium (QVA) combination therapy was found to be more effective than glycopyrronium and tiotropium in reducing mild exacerbations in severe COPD. QVA is only better than glycopyrronium and not tiotropium.[28]

➢ COMBINATION THERAPY USING LABA AND INHALED CORTICOSTEROIDS: For many years, inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs) have been used in combination to treat COPD. Numerous important randomized clinical trials have shown that this combination works better in terms of lung function, health status, and exacerbation risk.[29] When compared to once-daily tiotropium, the twice-daily regimen of salmeterol plus fluticasone propionate (SFC) shown comparable results on overall exacerbation rates. . Lung function has improved more when the LABA vilanterol and the ICS Fluticasone Furoate (FF) are taken together once a day than when they are taken separately.[30]

➢ BRONCHODILATOR WITH PDE-4 INHIBITOR: Theophylline, a medication with anti-inflammatory and bronchodilator qualities, is given orally together with inhaled bronchodilators to treat COPD, Theophylline is therapeutically useful at conventional or low doses; however, comprehensive research in this area is limited.[31] However, roflumilast, a PDE-4 inhibitor, roflumilast has been shown to minimize exacerbations; this may also be the case with LAMA combinations. Although further research is needed to confirm this notion, roflumilast seems to work better in those who are more likely to have exacerbations and may also change the phenotypic characteristics of patients who are more likely to have exacerbations.[32]

(A). PEDIATRIC COPD: Lung damage in a baby is indicated by chronic lung sickness in children. Because their lungs haven't had time to fully develop, premature babies are more likely to have these kinds of respiratory problems shortly after delivery. However, you can either cure or reduce the symptoms of CLD by using treatments for chronic lung diseases.

Figure 6: COPD in children.

- ❖ DIAGNOSIS: Your child may undergo a number of tests in order to get a diagnosis and track their treatment plan. A series of chest X-rays may reveal some lung abnormalities in youngsters. Another method of diagnosis is by blood tests that measure the oxygen concentration of the blood. Your doctor or medical team will check for symptoms of CLD, such as nasal flaring, rapid breathing, and other indications of lung inadequacy. Spirometry is a common lung test.
- ❖ MEDICATIONS: The management of chronic lung disorders may also involve the use of medications. To clear the airways, your doctor may recommend drugs like: {1} bronchodilators. {2} Corticosteroids are frequently used to reduce inflammation. {3} Diuretics are administered to prevent lung fluid accumulation. Newborns with CLD usually get better over time, though they could need a mechanical ventilator for a while. Improving comfort and breathing is the main objective of treatment for kids with long-term lung conditions.
- ❖ DIET: Nutritional supplements may be used in the treatment of chronic lung conditions. Since children with respiratory conditions eat a lot of calories, it's important to include extra proteins to ensure proper growth. Breathing and eating can be difficult for kids. To encourage healthy growth and development, children can be given high-calorie protein supplements through a tube.[33]

(B).GERIATRIC AND ADULTS ASSESMENT IN COPD: The combination of two maintenance drugs to control symptoms, enhance lung function, and lower the likelihood of exacerbations is known as dual therapy for individuals with Chronic Obstructive Pulmonary Disease (COPD). Combining a Long-Acting Muscarinic Antagonist (LAMA) with a Long-Acting beta-2 Agonist (LABA), frequently administered in a single inhaler, is the most common and advised type of dual therapy.

- ❖ DIAGNOSIS
- Medical History and Symptoms Review: The physician will discuss the patient's symptoms, such as chronic cough, shortness of breath, and mucus production. They will also review the patient's smoking history and exposure to environmental or occupational pollutants.
- Spirometry: This is a key diagnostic test where the patient breathes into a device called a spirometer. It measures the amount and speed of air the patient can exhale. A reduced airflow, especially after taking medication, helps confirm the presence of COPD and assess its severity.
- Chest X-ray: An X-ray can help rule out other conditions and provide visual information about the lungs and heart. It can show signs of emphysema or other lung abnormalities.
- Arterial Blood Gas (ABG) Test: This test measures the levels of oxygen and carbon dioxide in the blood to assess how well the lungs are functioning in terms of gas exchange.
- α -1 Antitrypsin Test: In cases where a genetic predisposition is suspected, this blood test checks for deficiency in alpha-1 antitrypsin, a protein that protects the lungs.

- ❖ MEDICATIONS: (LABA + LAMA), Tiotropium/Olodaterol, Umeclidinium/Vilanterol, Indacaterol/ Glycopyrronium, Glycopyrrolate/Formoterol, ICS + LABA, Bronchodilator + PDE4 Inhibitor.

- ❖ DIET: Increase Healthy Fats, Prioritize Lean Protein, Choose Complex Carbohydrates, Maintain Hydration, Monitor Salt Intake.

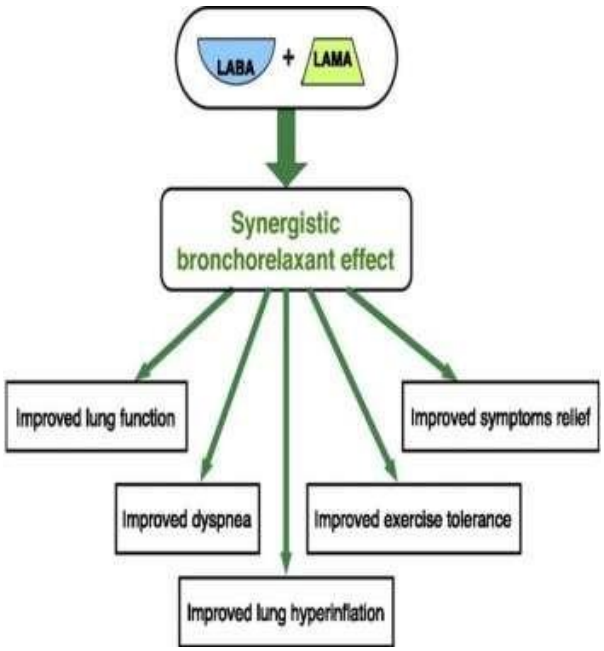

Figure 7: Action of LABA/LAMA.

TRIPLE DRUG THERAPHY: Triple inhaled therapy, which consists of an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting 2-agonist (LABA), is recommended for COPD patients who have significant symptoms despite previous treatment with an inhaled glucocorticoid-LABA or LAMA-LABA and who are at increased risk of frequent or severe exacerbations. Studies have indicated that triple therapy improves lung function and COPD symptoms more than dual therapy, although patients still need to use numerous inhalers multiple times a day. Studies have indicated that triple therapy improves lung function and COPD symptoms more than dual therapy, although patients still need to use numerous inhalers multiple times a day.[34] Triple therapy, which consists of an inhaled corticosteroid (ICS), a phosphodiesterase-4 (PDE-4) inhibitor, and a long-acting beta-agonist (LABA), is advised by the UK National Institute of Clinical Excellence (NICE) guidelines; nevertheless, there is conflicting evidence regarding its efficacy. Welte

et al. discovered in a carefully planned three-month study that adding budesonide and formoterol to tiotropium significantly reduced morning symptoms and exacerbations compared to tiotropium alone.[35]

➢ OPEN TRIPLE THERAPY: Open triple therapy has been shown to improve lung function, health status, the need for rescue medication, and the risk of Acute Exacerbations (AEs) as compared to ICS/LABA or mono LAMA therapy. The addition of a LAMA to ICS/LABA is known as open triple therapy.[36] The LABA/ICS combination contains a number of drugs, such as formoterol with budesonide and beclomethasone, which is available as a Dry Powder Inhaler and a Metered-Dose Inhaler with a 12-hour duration of action. Another combination with a 12-hour duration of action is formoterol/mometasone in MDI form. The duration of action of glycopyrronium bromide, marketed as DPI, is 12 to 24 hours. Tiotropium comes in both DPI and MDI forms and has a long half-life of 24 hours. Umeclidinium is available as a DPI and acts for 24 hours. Last but not least, glycopyrrolate has a half-life of 12 Hour.[37]

➢ CLOSED TRIPLE THERAPHY: ICS, LABA, and LAMA make up private triple combo therapy. It has been demonstrated that closed triple therapy reduces exacerbations and enhances quality of life more effectively than LABA/LAMA. Furthermore, they have been demonstrated to be superior than ICS/LABA in minimizing exacerbations and improving lung health, symptoms, and quality of life, particularly in ICS-responsive disorders.[34, 38] The most widely used closed triple-drug regimens are fluticasone/umeclidinium/vilanterol (DPI), beclomethasone/ formoterol/glycopyrronium (MDI), and budesonide/formoterol/ glycopyrrolate (MDI), all of which have 12 hr durations of action.[37]

The primary advantage of using a triple inhaler for COPD, aside from improved adherence, is that the LABA/LAMA will reduce symptoms and exacerbations by enhancing the bronchodilator's effects on the smooth muscle of the airway, while the ICS moiety will reduce exacerbations by lowering the eosinophilic component of inflammation.[39]

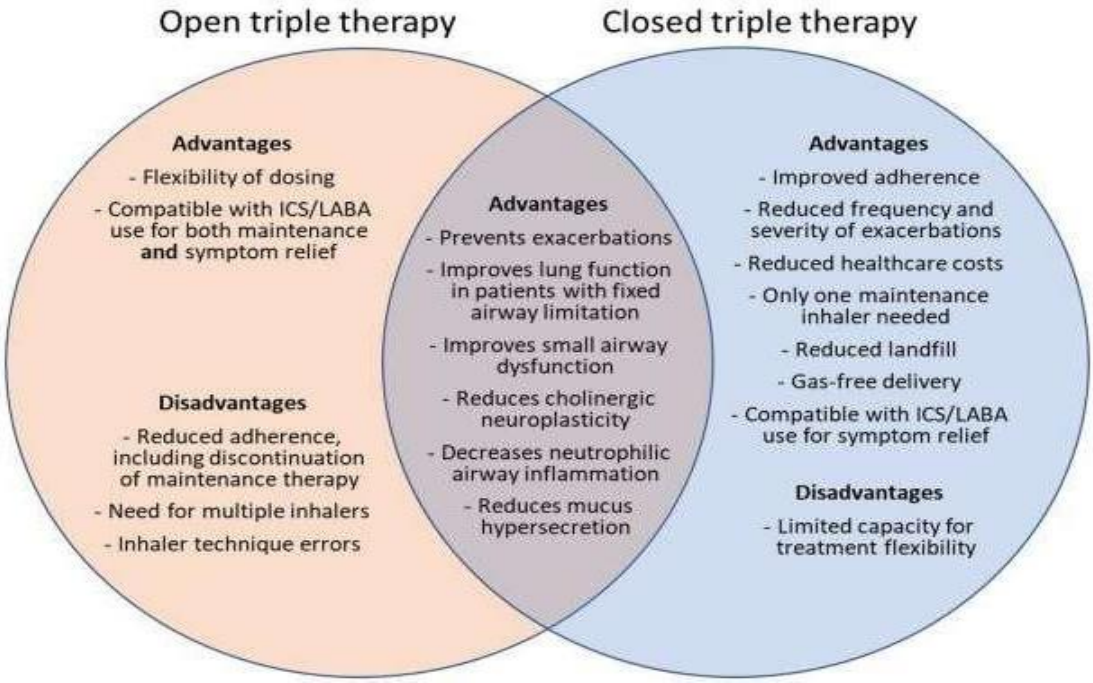

Figure 8: Comparision of open triple therapy and closed triple therapy.

COMPARISON OF DUAL AND TRIPLE COMBINATION THERAPY:

People who had triple remedy had been 25% much less in all probably than people who obtained twin remedy to enjoy moderate-to-excessive COPD exacerbations. The results were consistent whether the triple treatment was compared to ICS/LABA or LABA/LAMA. Regarding protective outcomes, there were no appreciable differences between triple and twin inhalers. For those getting twin inhaler medicine for frequent COPD exacerbations, triple remedy is suggested according with contemporary advice.[40] In contrast to other drugs, patients who start on a LAMA seem to have a good chance of switching to a triple therapy within 24 months; nevertheless, approximately 25% of those who were initially advised to start on a triple remedy seem to switch to LABA+ICS or LAMA within that time.[41] In comparison to both twin inhalers, the Informing the Pathway of COPD Treatment (IMPACT) trial, a large multicenter study comparing triple inhalers with unique twin inhalers, confirmed the prevalence of triple remedy with 15% and 25% reductions in signs and symptoms for ICS/LABA and LAMA/LABA, respectively. An immediate analysis of the ICS/LABA & LABA/LAMA

fingers within the equal trial found significantly fewer COPD exacerbations within the ICS/LABA arm, in contrast to the FLAME trial, which tested Indacaterol, Glycopyrronium, and Fluticasone for COPD and reported lower exacerbation quotes within the LABA/LAMA arm.[42] The GOLD recommendations encourage those with the most severe COPD to think about using a triple treatment. If an affected individual uses a lot of gadgets, there is a greater chance that they will utilize the incorrect inhaling technique. Furthermore, research has shown that individuals with COPD who use severe inhalers for treatment follow their regimens considerably less frequently than those who use unmarried inhalers. Because a single-inhaler treatment is easier to administer, it may also increase patient compliance, improve scientific results, and lessen COPD patients' desire for scientific resources. The financial and aid burden on healthcare can be reduced if those blessings are achieved without increasing costs. In terms of lung function, mortality, and the frequency of moderate or severe COPD exacerbations, patients with symptomatic COPD may benefit from triple therapy with inhalers, according to a meta-study analysis by Long et al. The clinical response and potential side effects following medication therapy adjustments should be assessed in order to guarantee optimal control and minimize side effects. If unfavorable results (such as pneumonia) arise, ICS must be stopped very away.[43]

		DELIVERY OPTIONS			
Generic Drug Name	Inhaler Type	Nebulizer	Oral	Injection	Duration of Action
BETA$_2$-Agonists					
Short-acting (SABA)					
Fenoterol	MDI	✓	pill, syrup		4-6 hours
Levalbuterol	MDI	✓			6-8 hours
Salbutamol (albuterol)	MDI & DPI	✓	pill, syrup, extended release tablet	✓	4-6 hours 12 hours (ext. release)
Terbutaline	DPI		pill	✓	4-6 hours
Long-acting (LABA)					
Arformoterol		✓			12 hours
Formoterol	DPI	✓			12 hours
Indacaterol	DPI				24 hours
Olodaterol	SMI				24 hours
Salmeterol	MDI & DPI				12 hours
Anticholinergics					
Short-acting (SAMA)					
Ipratropium bromide	MDI	✓			6-8 hours
Oxitropium bromide	MDI				7-9 hours
Long-acting (LAMA)					
Aclidinium bromide	DPI,				MDI 12 hours
Glycopyrronium bromide	DPI		solution	✓	12-24 hours
Tiotropium	DPI, SMI, MDI				24 hours
Umeclidinium	DPI				24 hours
Glycopyrrolate		✓			12 hours
Revefenacin		✓			24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)					
Fenoterol/ipratropium	SMI	✓			6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓			6-8 hours
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)					
Formoterol/aclidinium	DPI				12 hours
Formoterol/glycopyrronium	MDI				12 hours
Indacaterol/glycopyrronium	DPI				12-24 hours
Vilanterol/umeclidinium	DPI				24 hours
Olodaterol/tiotropium	SMI				24 hours
Methylxanthines					
Aminophylline			solution	✓	Variable, up to 24 hours
Theophylline (SR)			pill	✓	Variable, up to 24 hours
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)					
Formoterol/beclometasone	MDI, DPI				12 hours
Formoterol/budesonide	MDI, DPI				12 hours
Formoterol/mometasone	MDI				12 hours
Salmeterol/fluticasone propionate	MDI, DPI				12 hours
Vilanterol/fluticasone furoate	DPI				24 hours
Triple Combination in One Device (LABA+LAMA+ICS)					
Fluticasone/umeclidinium/vilanterol	DPI				24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI				12 hours
Budesonide/formoterol/glycopyrrolate	MDI				12 hours
Phosphodiesterase-4 Inhibitors					
Roflumilast			pill		24 hours
Mucolytic Agents					
Erdosteine			pill		12 hours
Carbocysteine†			pill		
N-acetylcysteine†			pill		

SAFETY OF DUAL AND TRIPLE COMBINATION DRUGS: Inhaled

bronchodilators are normally safe, but they can have predictable side effects that may necessitate modifying the course of treatment. Inhaled corticosteroids can cause local side effects such dysphonia (voice hoarseness) and candidiasis (yeast infection) due to a buildup in the mouth and throat. These can be decreased by utilizing different inhaler devices, washing the mouth after inhalation, or using spacer devices with metered dose inhalers. However, due to complicating factors such concomitant use of oral corticosteroids or the severity of the disease, it is more difficult to relate the more severe systemic adverse effects of inhaled corticosteroids to the medicine alone. It may be difficult to determine the risk of osteoporosis associated with using inhaled corticosteroids with considerable osteoporosis prevalence since severe COPD is associated with an elevated risk of osteoporosis. Using ICS raises the risk of a lower respiratory tract infection in people with COPD.[44] One of the more concerning side effects of inhaled corticosteroids, which has been observed with both newer and older drugs, is an increased frequency of clinically diagnosed pneumonia in COPD patients. The explanation for why inhaled corticosteroid treatment does not affect overall mortality or pneumonia-related mortality in COPD patients is unknown, despite this relationship.[45] Pneumonia risk was increased with ICS/LAMA/LABA FDC compared to LABA/LAMA FDC. It was unlikely that having pneumonia would increase one's probability of dying from all causes.[40] The baseline incidence of AECOPD is larger than the baseline incidence of pneumonia, according to Mammen and colleagues. When triple therapy is used instead of dual LABA/LAMA therapy, the reduction in the rate of COPD exacerbations is expected to be more clinically significant than the rise in the risk of pneumonia.[46] On the other hand, PDE-IV inhibitors could have bothersome gastrointestinal side effects include nausea and diarrhoea, as well as headache and sleepiness, unlike PDE-III blockers, which have serious adverse events such convulsions and ventricular tachycardia. Many times, these bad effects compel a sizable portion of patients to temporarily quit their therapy. PDE-IV inhibitors can promote weight loss, especially in obese patients, even if they do not cause major cardiac concerns. The weight loss typically resumes when the medication is stopped. Improved dosage schedules are being researched to possibly reduce these annoying side effects.[47]

DISCUSSION

Mix bronchodilator therapy and LAMA/LABA FDC drugs are likely to become the mainstay of treatment for certain individuals with symptomatic COPD, according to the current revisions to the GOLD guidelines. These therapies are often long-lasting and secure. When used in conjunction with bronchodilator single-dose medication, they have been shown to subtly reduce aircraft route deterrence. In any case, they reduce intensifications in the same way as LABA/ICS treatment without the extra risks associated with ICS. They also appear to increase PROs like QoL and dyspnea, but these improvements seem to be less robust at any given time when measured as mean changes in large preliminary data. Some patients will experience more severe clinical side effects from these medicines than others. It is important that the range and degree of clinical improvements demonstrated in clinical preliminary findings align with the desires of both the patient and the physician. Rules are an invaluable resource for physicians seeking to treat their patients appropriately. Ultimately, a variety of considerations influence the choice of treatment. Physicians must consider physiology, severity and frequency of intensification, proximity of converging findings, and tolerating explicit indications. The cost and accessibility of inhalers frequently influence the choice of treatment. Despite all, choosing the best course of action for a single patient necessitates careful consideration of these factors, careful monitoring to determine physiological and symptomatic response, and a willingness to adjust treatment based on response.The majority of patients diagnosed with COPD need not receive triple treatment because the dominant part of the disease has few symptoms, little probability of worsening, and may be managed with non-pharmacological interventions. However, even though this isn't in line with GOLD, EMA, or FDA recommendations, people who continue to have symptoms during bronchodilator support treatment, had a moderate-to-severe compounding in the previous year, had a rapid decline in lung function, or had a previous analysis of asthma or covering qualities with asthma may, as we would like to believe, be candidates for a preliminary with triple treatment. In contrast to dual dosage and single dose inhalers, the potential of triple dose single inhalers is evident from a variety of studies, researches, preliminary reports, and surveys containing experimental data.

CONCLUSION

Compared to dual therapy (inhaled corticosteroids and LABA or LAMA and LABA) or LAMA monotherapy, triple therapy was associated with a lower rate of moderate or severe COPD exacerbations as well as improved lung function and health-related quality of life in this meta-analysis of COPD patients. Triple therapy, however, did not improve patient survival and may increase the risk of pneumonia. Therefore, triple therapy should only be administered to patients with more severe COPD symptoms that dual therapy cannot adequately treat. This study suggests that triple therapy (LABA + ICS + LAMA) may be more beneficial for patients with severe COPD than dual therapy (LABA + ICS). The study demonstrated that triple-drug therapy outperformed dual-drug therapy in the treatment of COPD due to the significant increase in lung function and ensuing reduction in the frequency of exacerbations. With a balanced baseline characteristic ensuring the validity of the comparison, the results strongly supported the preferable use of triple therapy, especially for patients

with severe disease or frequent exacerbations. The number of persons with severe COPD is also decreased with triple treatment. The improvement in lung function and the reduction of symptoms led to an improvement in the patients' quality of life. In order to enhance patient outcomes and effectively manage the progression of COPD, this research highlights the importance of tailored, escalated therapy regimens and supports current therapeutic guidelines.

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