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Review Article

POTENTIAL DRUG DELIVERY SYSTEMS AND DEVICE COMBINATION FOR THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

PREETHI S.[1], PRAVEEN HALAGALI[1,2], SURYA CS[1], VIKAS JAIN[1*]

[1]Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru-570015, Karnataka, India. [2]Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal-576104, Karnataka, India

*Corresponding author: Vikas Jain; *Email: vikasjain@jssuni.edu.in

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) presents with chronic lung inflammation and poorly reversible airflow limitation, necessitating bronchodilators for management. The Global Initiative for COPD recommends combining Long-Acting Beta-Agonists (LABAs) and Long-Acting Antimuscarinic Agents (LAMAs) for most COPD patients. Developing fixed LAMA/lABA combinations is crucial. Adding an Inhaled Corticosteroid (ICS) to this combination may offer additional benefits, including preventing exacerbations. The GOLD report emphasizes diagnosis, prevention, exacerbation management, and addressing comorbidities. It advocates for holistic COPD management, integrating pharmacologic and non-pharmacologic approaches. Novel strategies like mono, dual, and triple therapies are recommended. The review highlights COPD's impact on COVID-19, comorbidities, and relevant patents concerning COPD and bronchodilators. The bronchodilator treatments may improve their efficacy in this critical aspect of COPD. Research shows that dual bronchodilation improves lung function and symptoms more consistently than mono-bronchodilation while potentially lowering the risk of exacerbations and disease deterioration and having a similar safety profile.

Keywords: Bronchodilators, GOLD, LABA, LAMA, Triple therapy

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INTRODUCTION

According to World Health Organization (WHO) data, Chronic Obstructive Pulmonary Disease (COPD) is ranked as the third greatest cause of mortality, causing 3.23 million deaths worldwide, accompanied by increased morbidity and mortality, as well as massive human suffering and financial loss. COPD is a highly complex infectious lung disease marked by decreased airflow and airway inflammation. COPD is becoming more common around the world. It rises in the aged population ages as well as when exposed to more risk factors [1]. COPD is also known as smoker cough because tobacco smoke is a major risk factor. COPD causes recurrent lung infections, hastening the destruction of lung tissue [2, 3]. Comorbidities like hypertension, lung cancer, diabetes, coronary artery disease, and depression exacerbate symptoms in the later stages of the disease. COPD can be disrupted by episodes of respiratory symptoms that cause acute worsening (referred to as "exacerbations"), which leads to the majority of the total COPD burden [4]. The presence and severity of symptoms can vary symptoms are dyspnea, chronic cough progressive, and the production of sputum. Spirometers such as the forced expiratory volume (FEV_1) in one second can detect COPD that is worsening over time, though the disease can worsen at different rates. It has become very challenging to manage COPD, including disease variation and underreporting of symptoms. The prevention and management of COPD are called the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document. The GOLD document was published in 2023 and recommended that treatment has to be chosen depending on the severity of symptoms as well as exacerbation. When exacerbation rates are high, treatment is based on a LAMA (long-acting muscarinic antagonist) or a combination of LAMA/lABA (long-acting β2 agonist) if symptomatic [5]. The challenges in COPD are (a) The cardiovascular risk of COPD Since COPD patients are more likely to have cardiovascular death or morbidity regardless of other risk factors, such as tobacco smoking, the high prevalence of CHF in these individuals is not surprising. (b) Identifying chronic heart failure (CHF) when COPD flares up It has recently been evaluated that monitoring the plasma levels of B-type natriuretic peptide (BNP) in patients who arrive at the emergency room with dyspnea is a diagnostically beneficial procedure. (c) Finding CHF in individuals with stable COPD Because Echocardiography seems to be a more accurate method than BNP levels for detecting unexpected LV systolic dysfunction in individuals with stable COPD, as 20% to 25% of ambulatory patients with CHF had BNP values of 100 pg/ml [6]. The articles selected for the present review article were reviewed from several scholarly databases, such as Taylor and Francis, Elsevier, PubMed, ScienceDirect, Google Scholar, Nature, etc., in chronological order. The search strategy included keywords such as *Bronchodilators, GOLD, LABA, LAMA, Triple therapy*, which are organized in chronological order to structure the review article comprehensively.

Pharmacology of COPD

Limitation in the airflow, which is chronic, is a major characteristic of COPD that is caused by a combination of pathological processes such as airway narrowing, the loss of small conducting airways, and mucus hypersecretion. When a person breathes, the air passes down the trachea and into the airways found in the lungs, known as the bronchial tubes. These tubes further branch out into many short, thinner tubes known as bronchioles inside the lungs. Bunches of tiny circular air sacs called alveoli are at the end of these tubes. Healthy air sacs are stretchy and elastic. These air sacs fill like a balloon as a person breathes in, and the air sacs flatten as they breathe out. Energy is needed to blow up the air sacs, but no energy is required to empty them as it return to their original size. COPD cases have less airflow capacity, which can be related to several reasons, such as air sacs and airways losing stretchiness, weakening of the air sac walls, inflammation and thickening of airway walls, and clogging of airways due to more mucus production [7, 8]. COPD comprises two primary conditions: chronic bronchitis, emphysema, or both [9]. The different stages of COPD cases as shown in fig. 1.

Role of anti-inflammatory drugs and bronchodilators in the treatment of COPD

Bronchodilators

The long-acting bronchodilators-long-acting β2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs)-represent the basis of management with enough ability to relieve bronchial obstruction and improve airflow in COPD. They act by relaxing the smooth muscles of the airways, hence reducing hyperinflation and activating lung function, thus diminishing dyspnea and increasing exercise capacity. Fixed-dose combinations of LABAs and LAMAs have been proven to be superior to monotherapy because of their efficacy in controlling symptoms and preventing exacerbations [10].

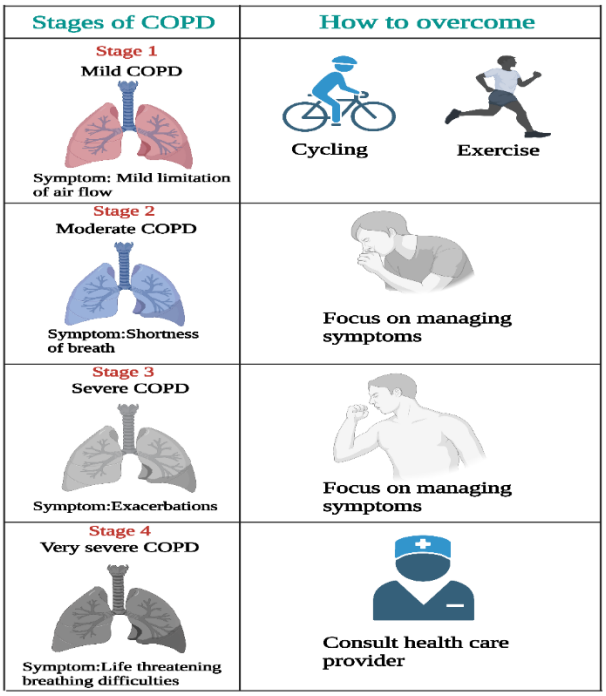

Fig. 1: The stages of COPD [9]

Anti-inflammatory agents

Inhaled Corticosteroids (ICS) are not recommended as a sole and single-agent therapy for COPD; however are of benefit when combined with bronchodilators-particularly in patients with a history of frequent exacerbations. New anti-inflammatory strategies have yet to be fully explored, including mixed PDE3/4 inhibitors, which aim to offer both bronchodilation and anti-inflammatory effects within a single treatment [11].

Treatment strategies

COPD pharmacological treatment aims to avoid exacerbations and help relieve symptoms, hence reducing the activity of the disease, stopping the progression of the disease, as well as eventually, limiting the impact of the disease, which can be fulfilled through risk factor control, pharmacological treatment as shown in fig. 2 [12, 13].

Control of risk factors

As a part of the prevention and treatment of COPD, the risk factors are critical to recognize and decrease. Smoking cessation, for example, is a critical intrusion, so smoking cessation messages and interventions are required. Tobacco dependence treatments, like sustained-release bupropion, varenicline, nortriptyline, nicotine inhalers, nicotine gum, nicotine patches, and nicotine nasal sprays, can be impactful as abandoning aids if potential complications are not present [14].

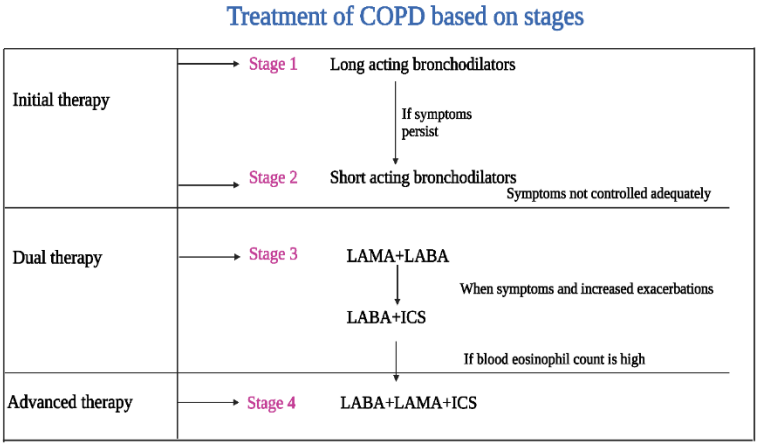

Fig. 2: Stage-based treatment of cases with COPD [12, 13]

Nonpharmacologic management

Nonpharmacological management includes lowering subjecting to pollution indoors and outdoors, such as occupational inhalants and biomass fuel, as well as taking individual protective measures. Exacerbations, COPD hospitalizations, and all-cause mortality are all reduced by regular physical activity [15].

Non-pharmacological interventions are paramount in managing chronic obstructive pulmonary disease (COPD) as they represent an integral part of efforts to achieve the best patient outcomes. This gives rise to significant points of meaning: (a) Holistic Treatment: COPD itself is a systemic disease presenting different symptoms, including muscle dysfunction and psychological problems. Non-

pharmacological alternatives, such as smoking cessation, pulmonary rehabilitation, and nutritional support, provide further management of the disease aspects that other management options do not address at all. (b) Improved Quality of Life: Studies show that pulmonary rehabilitation significantly improves health status and quality of life for COPD patients. It covers exercise training, education, and psychosocial support. All these aspects are pivotal in the management of symptoms and, therefore in enhancing functionality in daily life [16].

Pharmacological treatment

The symptoms can be treated by reducing the severity and frequency of exacerbations, improving tolerance to exercise, health status as well as the application of pharmacologic therapy. The ABE assessment scheme is used to perform an individualized assessment of symptoms and exacerbation risk after the spirometry and clinical diagnosis of COPD are confirmed [17, 18]. Based on the COPD stage, depicts the initial treatment options for COPD and progresses to a combinational and advanced therapy (triple therapy) approach [19]. The GOLD 2023 provides information on COPD diagnosis, prevention, and treatment methods. The "ABE" assessment of COPD cases, which focuses on the intensity of symptoms (as evaluated by a questionnaire) and the risk of exacerbation, is currently supported by the GOLD [20]. GOLD group patients had mild symptoms and a low risk of exacerbation. Patients in the GOLD group B experienced severe symptoms but a lower chance of exacerbation [21]. Patients in GOLD group E have a moderate exacerbation or lead to hospital [22].

Monotherapy treatment for COPD

Bronchodilators are divided into three categories: muscarinic receptor antagonists, xanthine, and β2-adrenoceptor (AR) agonists used alone or in combination. All recommendations and guidelines, therefore, emphasize that inhaled bronchodilators are the backbone for all the levels of COPD stages [23, 24].

Short-acting bronchodilators

Short-acting bronchodilators with a fast onset of action are recommended for immediate relief at very early stages. These short-acting agents relax the muscles in the airways and make it easier for the patient to inhale properly [25].

Long-acting bronchodilators

Long-acting bronchodilators can be recommended based on symptom seriousness. Long-acting bronchodilators are recommended as the first line of treatment for symptomatic COPD, according to new recommendations [26]. Table 1 shows the approved LAMA and LABA monotherapy drugs for stage 1 and stage 2 as a first-line therapeutic approach for COPD cases.

Table 1: Approved long-acting bronchodilator as monotherapy for COPD

Generic name	Drug class	Drug dose	Type of dosage form	Inhaler device
Aclidinium bromide	LAMA	400 µg (1 inhalation) twice a day	Dry powder	Pressair [27]
Arformoterol tartrate	LABA	15 µg/2 ml (1 inhalation with a standard jet nebulizer) twice a day	Inhalation Solution	Nebulizer [28]
Formoterol fumarate	LABA	20 µg/2 ml (1 inhalation with a standard jet nebulizer) twice a day	Inhalation Solution	Nebulizer [29]
Glycopyrrolate	LAMA	15.6 µg/capsule twice a day	Inhalation powder	Neohaler [29]
Indacaterol	LABA	75 µg (per actuation) once daily	Inhalation Powder	Neohaler [30]
Olodaterol	LABA	5 µg/dose (1 dose= 2puffs) once daily	Inhalation Spray	Respimat [31]
Salmeterol	LABA	50 µg (1 inhalation) twice a day	Inhalation Powder	Discus or MDI [32]
Tiotropium	LAMA	18 µg (1 inhalation) twice a day	Dry powder inhaler	Respimat or Handihaler [33]
Umeclidinium	LAMA	62.5 µg/inhalation Once daily	Dry powder inhaler	Ellipta [34]

Effect of inhaled medicines on bronchodilation against airflow limitation

The smooth muscle of the airways' beta-2 adrenergic receptors is activated by LAMA, whereas the muscarinic receptors are blocked by LABA. These receptors can be activated or blocked to produce bronchodilation, which relaxes the smooth muscle in the airways and improves airflow.

Long-acting β2 agonist

LABAs are a type of bronchodilator that causes relaxation and dilatation of the airways in the lungs, making it simpler to breathe. LABAs relax the smooth muscle by stimulating β2-adrenergic receptors and are available in dosage forms such as nebulizers, metered-dose inhalers, injected pills, dry powder inhalers, and syrup [35]. Long-acting type aids in the prevention of breathing problems, while the short-acting type relieves symptoms. Short-acting β2-agonists are used to treat people with steady COPD who have intermittent symptoms [36].

Long-acting muscarinic antagonist

Potent bronchodilators called muscarinic antagonists, commonly referred to as anticholinergic drugs, are used to treat COPD, reduce dyspnea, and improve exercise tolerance. They inhibit acetylcholine-mediated bronchoconstriction by binding to M3 receptors in the smooth muscle of the airway [37]. For maintenance therapy, some LAMA/device systems with varying characteristics and doses are available currently. They improve lung function and decrease acute bronchial exacerbations while remaining safe [38].

Long-acting β2 agonist+ICS

Activating beta-2 adrenergic receptors is the main way that LABA causes bronchodilation; they have no anti-inflammatory properties. However, LABA and ICS complement each other well. While ICS reduces inflammation by inhibiting pro-inflammatory pathways, LABA causes bronchodilation by activating beta-2 adrenergic receptors. By addressing inflammation and bronchoconstriction jointly, they lessen exacerbations [39].

Long-acting muscarinic antagonist+ICS

By inhibiting muscarinic receptors, LAMA causes bronchodilation and decreases bronchoconstriction. They cooperate to treat both bronchoconstriction and inflammation, lowering exacerbations when combined with ICS, which have anti-inflammatory actions by inhibiting pro-inflammatory pathways.

Dual therapy treatment for COPD

ICS with LABA for dual therapy in a fixed-dose combination (FDC)

Based on the limited efficacy of ICS monotherapy on relevant outcomes, it is not recommended in COPD, unlike asthma. However, it is seen to reduce symptoms, specifically when given LABAs. ICS+LABA is primarily used in high-risk symptomatic COPD patients with significant airflow restriction to prevent exacerbations and combinations are listed in table 2**.** The moderate to severe exacerbation rates, however, were comparable between LABA/ICS and LABA monotherapy, as they were in the TRISTAN study (trial of inhaled steroids and long-acting β2-agonists) [40].

Table 2: Combination of LABA with ICS in a fixed-dose inhaler

Active principle		Dose per actuation	Onset of action	References	Approved country
ICS	LABA				
BDP	FF	100 µg of BDP and 6 µg of FF (2 actuations at a time) BID	1-3 min	[41]	Europe, Australia, and UK
FP	S	250 µg of FP and 50 µg SX (1 strip BID)	15-20 min	[42]	US
B	FF	160 µg of B and 4.5 µg of FF (2 actuation) BID	5 min	[43]	US
FLF	VT	1strip contains 100 µg of FLF and 25 µg of VT once daily	5 min	[44]	Europe and US
M	FF	200 µg of M and 5 µg of FF (also available in 100/5 µg) 2 actuations BID	5 min	[45]	US

Abbreviations: BID: Twice-daily BDP beclometasone dipropionate; B (budesonide); M (mometasone) and once-daily FLF/VT (fluticasone furoate/Vilanterol). ICS/lABA combo consistently decreases the rate of exacerbation in high-risk cases with FEV1<50%.

Rationale for combining LAMA and LABA

For the treatment of COPD, combining two distinct types of long-acting bronchodilators with various mechanisms of action decreases dose-related side effects and improves patient-related results [46, 47]. According to NICE (National Institute for Health and Care Excellence) recommendations, LAMA/lABA therapy is advised for COPD patients whose symptoms don't improve or go away with LABA therapy alone, while the combination of LAMA/lABA is not prescribed for those who are already taking LAMA as single maintenance therapy [48–50]. This recommendation, however, is certainly surpassed by current findings that the frequent addition of β2 agonists to anti-muscarinic not only elicits higher bronchodilation than LAMA alone but also greatly enhances many reported results [51, 52]. Other dual long-acting bronchodilator therapies are LABAs/lAMAs used for COPD are listed in table 3.

Table 3: A fixed-dose combination of LABA and LAMA

Drug combo	Manufacturer	Dose per puff	Approved country
Formoterol fumarate/aclidinium	Circassia Pharmaceuticals	340 µg aclidinium and 12 µg formoterol fumarate (1 inhalation BID) [53]	US and Europe
(Indacaterol/glycopyrrolate)	*Sunovion*	27.5 µg Indacaterol and 15.6 µg glycopyrronium per capsule (BID) [54]	Europe
Stiolto Respimat Olodaterol/tiotropium	Boehringer Ingelheim	2.5/2.5 µg (2 puffs at a time) once daily [55]	US, Japan, China and Europe
Anoro Ellipta Vilanterol/Umeclidinium	GSK	2 Blister strips with 25 µg of Vilanterol and 62.5 µg of Umeclidinium (once daily) [56]	US, Canada, Japan, and Europe
Bevespi Aerosphere Glycopyrrolate and formoterol fumarate	AstraZeneca Pharmaceuticals	9 µg of glycopyrrolate and 4.8 µg formoterol (inhalation BID) [57]	US

Triple therapy treatment for COPD

Triple therapy using a single inhaler: LAMA+LABA+ICS

Through coformulation with novel ICSs, the creation of once-daily dual-action LABA+LAMA combination medicines may pave the path for better "triple treatment" combinations [58]. Treatment regimens can be made simpler by merely utilizing these therapeutic techniques once each day. The investigation of triple therapy with a LAMA/lABA/ICS combination, which is considered an emerging approach, has shown benefits when compared to monotherapy and dual drug therapy inhalers on lung function [59]. Triple therapy combined with pulmonary rehabilitation has been beneficial for lung function, which was seen during a pilot study on cases with COPD [60]. With this triple therapy, the combination of the dose of each agent can be optimized [61].

Triple dose inhaler

Evidence indicates that simplifying treatment strategies can improve treatment adherence and persistence for COPD, potentially resulting in improving primary outcomes related to health affected by the discontinuation of treatment [62, 63]. The triple-drug inhaler is chosen over monotherapy and dual therapy for the following reasons: firstly, the symptoms of COPD are more controlled [64]. Second, for dual-drug single inhalers, the dose-dependent adverse drug reaction is an issue that can be resolved by using a triple-drug inhaler [65]. Third, some studies even showed that cases with high blood eosinophil levels, which affect lung function, can be treated by triple drug inhaler [66, 67].

Study protocol with registered clinical trial number

Treatment with triple therapy is limited to a selected number of individuals (symptomatic cases) who tend to be exacerbated despite the use of a dual inhaler (LAMA+LABA) [68, 69]. To evaluate the efficacy of the triple-drug inhaler, several clinical trial studies have compared the effect of the three-drug combination over the dual inhaler, as listed in table 4 [70].

A clinical trial registered for a combinational method is the IMPACT study protocol, which evaluated the effectiveness of once-daily FLF/UMC/VT triple medication therapy with FLF/VT and UMC/VT dual drug therapy [77]. The IMPACT study also reported that no such difference was observed between triple therapy and dual therapy containing UMC/VT in cases with blood eosinophil numbers less than 100 µl. However, an eosinophil level above 100 µl was associated with increasingly greater differences in therapy in favor of UMC/FF/VT. This indicates that smoking status and eosinophil blood count have the potential to use ICS in clinical practice along with survival benefits in cases with a history of exacerbation [78–80].

Table 4: Study protocol with the registered clinical trial number

Study protocol	NCT number	Comparative information
Trinity	NCT01911364	Compared triple therapy with dual therapy and ICS/lABA+LAMA [71, 72]
Tribute	NCT02579850	Compared the efficacy of dual therapy with extra fine triple-drug therapy [73]
Impact	NCT02164513	Compared triple-drug FDC with ICS+LABA and LAMA+LABA [74]
Fulfil	NCT02345161	Compared the effect of triple drug combination with ICS+LABA [75]
Kronos	NCT02497001	Used cosuspension technology for delivery and assess the effect of ICS+LAMA+LABA with dual therapy [76]

Advantages of triple therapy over dual therapy

Evidence gathered so far on triple-drug inhalers demonstrated that employing triple-drug therapy had advantages over LAMA/lABA, ICS/lABA, or single-drug therapy for airflow limitation with moderate to severe symptoms and a high chance of exacerbations (at least one). However, according to GOLD report 2023, the use of LABA+ICS in COPD is no longer encouraged. If there is an indication for an ICS, then LABA+LAMA+ICS is superior to LABA+ICS and is, therefore, the preferred choice. Such criteria can be used confidently to reduce the number of exacerbations [81, 82] Nevertheless, large retrospective studies reported that COPD cases with one exacerbation compared to cases with no exacerbation history had a higher rate of exacerbation in the following year, while KRONOS was shown to be effective in minimizing exacerbation in symptomatic cases with no exacerbation history. The eosinophil blood count is one of the factors that may support the effectiveness of treatment [83, 84]. The GOLD guidelines also followed this definition, which also introduced the specifications as follows:

i. LABA+LAMA+ICS treatment in cases with eosinophil counts more than 300 μl^{-1}

ii. LABA+LAMA bronchodilator combination in cases with eosinophils less than 100 μl^{-1} [85]

Symptomatic cases with FEV_1 less than 50%, severe exacerbation ($\geqslant$1), and eosinophil levels of more than 300 μl^{-1} have a higher risk of recurrent exacerbation and chances of hospitalization [86–88]. Thus, a triple-drug single inhaler should be considered as a first-line treatment for the first three months, and withdrawing the ICS from the regimen should be considered [89]. The addition of roflumilast (particularly in patients with chronic bronchitis and an FEV1<50% predicted) or a macrolide (particularly in patients who are not current smokers) may be considered [90].

Overview of COPD drugs

Chronic obstructive pulmonary disease is first managed with a combination of corticosteroids, bronchodilators, and other devices, managing symptoms and reducing periodic-attack cases. The table below summarizes specific drugs for COPD, including mechanisms and therapeutic outcomes. The drugs used in COPD are given in table 5 [91].

Pharmacological limitations of current treatments present across different stages of COPD

Modifying the disease will remain a useless affair; the current drugs, bronchodilators, and corticosteroids do not vary significantly in their effect on arresting the disease process, nor do they greatly affect outcomes such as lung function decline and mortality. Their purpose, primarily, is symptom relief and to decrease exacerbations. Disease modification is inconsistent: Efficacy of some treatment modalities may improve the symptoms and quality of life, but usually modestly, leaving enough reason to look for options that are of greater efficacy. Problem with ICS: ICS usage has been rampant even when physicians consider the patients not appropriate for such treatment, not differentiated with common route administration. Prolonged time results in profound side effects such as pneumonia and osteoporosis [96].

Limitations of inhaler devices

Current inhaler devices are greatly limited concerning deposition and patient compliance. Many patients do not use proper inhaler techniques, leading to reduced drug delivery; studies show up to 94% of patients never used their inhalers correctly, leading to poor disease control and increased healthcare costs. Functional limitations in today's pressurized metered-dose inhalers (pMDIs) arise due to the requirement for immediate organization of inhalation and actuation; improper timing can drastically reduce the amount of medication delivered34. Different inhalers require different techniques, which may contribute to confusion and noncompliance on the part of patients [97]. A comparative table of current and proposed drug delivery systems for chronic obstructive pulmonary disease, including their mechanisms, effectiveness, and ease of use is given in table 6.

Table 5: Drugs used in COPD

Drug class	Drug name	Mechanism of action	Therapeutic outcomes	References
Bronchodilators	Tiotropium Bromide	Long-acting anticholinergic that inhibits M3 receptors, leading to bronchodilation.	Increases FEV1, decreases dyspnea, improves exercise tolerance, reduces exacerbations	[92]
	Formoterol	Long-acting beta-agonist that relaxes bronchial smooth muscle by stimulating β2 receptors.	Improves lung function and reduces exacerbation rates	[93]
	Salmeterol	Long-acting beta-agonist similar to formoterol but with a longer onset of action.	Enhances airflow and reduces the frequency of exacerbations	[94]
Inhaled Corticosteroids	Budesonide	Reduces airway inflammation by inhibiting multiple inflammatory cytokines.	Decreases the frequency of exacerbations and improves health status	[95]
	Fluticasone Propionate	Similar action to budesonide; reduces inflammation in the airways.	Improves lung function and quality of life	[94]

Table 6: A comparative table of current and proposed drug delivery systems for chronic obstructive pulmonary disease, including their mechanisms, effectiveness, and application

Drug delivery system	Mechanism	Effectiveness	Application	References
Conventional Inhalers (MDIs, DPIs)	Deliver medication directly to the lungs via inhalation.	Effective for symptomatic relief but limited in addressing disease progression.	Requires proper inhalation technique; can be challenging for some patients.	[98]
Nebulizers	Convert liquid medication into the mist for inhalation.	Good for delivering larger doses; effective in acute situations.	Generally easy to use but less portable and requires cleaning.	[99]
Nanoparticles (NPs)	Encapsulate drugs and target delivery to specific lung tissues, allowing controlled release.	Higher bioavailability and specificity, potentially improving therapeutic outcomes and reducing side effects.	User-friendly; can be integrated into inhalation devices for ease of use.	[100]
Liposomes	Spherical vesicles that encapsulate drugs, enhancing delivery to lung tissues while minimizing systemic exposure.	Effective in increasing drug efficacy and reducing side effects	Easy to administer via inhalation; compatible with existing delivery devices.	[101]
Micelles	Formed from amphiphilic molecules, they enhance the solubility and stability of drugs for pulmonary delivery.	Improve pharmacokinetics and prolong drug action in the lungs	Simple administration can be used in standard inhalers.	[101]

Patents related to COPD

The various databases, including Espacenet, Google Patents, USPTO, and WIPO search engines, were used to conduct the document search. Searches in several databases were conducted using terms like COPD and bronchodilators like long-acting and short-acting. Some patents on the Bronchodilators were considered for this review are listed in table 7 [102].

Table 7: Patents on COPD and bronchodilators

S. No.	Drug name	Patentee	Patent application number	Category/Mechanism of action	Application of the patent
1	Petasites sp.	Axel Brattstroem	WO2006000119A1	Extract of *Petasites sp.* for use in veterinary medicine	Both humans and horses with COPD have shown improvement when treated with an extract from Petasites sp. The recommended daily dosage is between 1 and 50 mg/kg or more. When using corticosteroids is neither acceptable nor practical, this innovative approach is especially beneficial for horses. Patients with COPD can benefit from the manufacture of medications using the extract of Petasites sp.
2	Opioids for the treatment of "pink puffer" type of COPD. Opioid agonists are used to relieve symptoms like dyspnea	Wolfgang Fleischer Karen Reimer Petra Leyendecker	US20140057933A1	Opioid agonists like morphine, oxycodone, hydromorphone, propoxyphene, nicomorphine, dihydrocodeine, diamorphine, papavereturn, ethylmorphine, phenylpiperidine, methadone, dextropropoxyphene, buprenorphine, pentazocine, tilidine, tramadol, hydrocodone, codeine.	The goal of the current invention is to create an opioid-controlled release oral dosage form that contains at least one opioid and is used to provide medications for patients suffering from chronic obstructive pulmonary disease.
3	Methods of treating chronic obstructive pulmonary disease	Joel Cooper, Bryan Loomas, Don Tanaka, Michael Laufer, David Thompson, James Davenport, Gary Kaplan, Dave Haugaard, Glendon French	US20050085801A1	Improving a person's expiration cycle by changing the gas flow inside a lung	An implant is inserted into a lung's airway to enable expired air to exit the lung tissue, hence increasing gaseous flow in a lung suffering from chronic obstructive pulmonary disease.
4	Cannabinoids	Geoffrey Guy Philip Robson	US20090197941A1	cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC)	The innovation deals with treating COPD with a mixture of cannabinoids. The ideal cannabis combination is delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The cannabinoids should ideally be in a specified weight ratio of roughly 1:1 between CBD and THC.
5	Muscarinic antagonists	William Gerhart	WO2009134524A3	Inhalation solutions	Inhalation systems designed to deliver muscarinic antagonists for the management of respiratory conditions, including COPD.
6	Formoterol+budesonide	**Michiel Ullmann**	WO2015173154A1	Combination of inhaled corticosteroids and $\beta_2$agonist in a single device	The invention provides budesonide and formoterol, or its pharmaceutically acceptable salt, in a fixed-dose composition. This mixture is designed to treat COPD over the long term as well as to control acute exacerbations of the disease. Pro re nata, or p. r. n., is administered as a rescue drug designed to treat acute exacerbations of COPD, along with a maintenance dose for ongoing treatment.
7	Tolazoline	Alvaro H. Skupin	US5096916A	Imidazoline derivative, vasodilator and an α-adrenergic blocking agent. Sprays or powder for inhalation; Aerolised or nebulized preparations generated by other means the thermal energy for inhalation via a dry powder inhaler.	This is a treatment strategy for asthmatic COPD, which involves giving a patient an alpha-adrenergic blocking agent by inhalation in a dosage that reduces the respiratory distress associated with the disease.
8	Glycopyrrolate bromide	SauroBonelli, Francesca Usberti, Enrico Zambelli	WO2011076842A3	Stable aerosol solution formulations	Glycopyrronium bromide-containing stable aerosol solution formulations for COPD and other respiratory patients' use are the subject of this invention.
9	Fluticasone furoate	Neil Christopher Barnes, Steven John Pascoe	WO2015181262A1	Used for cases that possess a blood eosinophil count of>150 cells/µl.	The invention relates to pharmaceutical goods that treat patients with COPD, specifically those who have been diagnosed with an eosinophil blood count of 150 cells/µl, by using fluticasone furoate. According to preset criteria, the patients are identified as responsive, and the pharmaceutical product containing fluticasone furoate is then given to the selected patient.
10	Methods and systems for monitoring, diagnosing, and treating chronic obstructive pulmonary disease	Katrina Steiling, AvrumSpira, Marc Lenberg, Stephen Lam	US10533225B2	98 newly discovered genes that are expressed in the respiratory tract epithelium and can be used as biomarkers to gauge COPD	Offers a set of 98 genes that are expressed in the epithelium of the respiratory tract and act as biomarkers to gauge the severity of COPD. It comprises systems for expression-based COPD disease state categorization as well as techniques for classifying COPD status based on gene expression patterns. The program also provides treatment methods for COPD, highlighting potential improvements in the disease's diagnosis, categorization, and individualized care.

Table 8: Clinical trials on COPD [103]

NCT number	Study title	Study status	Phases	Study type	Start date
NCT06652776	The Italian Registry of Patients with Chronic Obstructive Pulmonary Disease	Enrolling_by_invitation		Observational	2024-09-30
NCT03044847	The Cohort Study for Chronic Obstructive Pulmonary Disease (COPD) in China	Enrolling_by_invitation		Observational	2016-07
NCT05480176	The China National COPD Screening Program	Recruiting		Observational	2021-10-09
NCT02024737	SILO2 (Signal Intensity Lung washout)	Completed		Observational	2014-02
NCT03071731	Glittre ADL-test: Responsiveness to Acute Bronchodilation in Chronic Obstructive Pulmonary Disease (COPD)	Unknown	NA	Interventional	2017-04-13
NCT01037387	Effect of Noninvasive Ventilation on Physical Activity and Inflammation in COPD Patients	Recruiting	PHASE4	Interventional	2025-12
NCT02008162	Bronchoreversibility and Radiologic Morphology of Emphysema	Unknown		Observational	2009-11
NCT03984188	Effectiveness of Low-Dose Theophylline for the Management of Biomass-Associated COPD	Completed	PHASE3	Interventional	2021-02-23
NCT01892488	Study to Demonstrate That Antibiotics Are Not Needed in Moderate Acute Exacerbations of COPD	Completed	PHASE4	Interventional	2013-06-07
NCT03450603	Predicting Risk Factors for Exacerbation of Chronic Obstructive Pulmonary Disease	Recruiting		Observational	2017-12-10
NCT06495047	Assessing Optimal Inhaler Strategies During Acute Exacerbations of COPD (AECOPDs) Using Oscillometry	Recruiting		Observational	2024-07-19
NCT02691988	Withdrawal of Inhaled Corticosteroids in Primary Care Patients With COPD	Unknown	NA	Interventional	2015-12
NCT03791658	Assessment of Adherence to Controller Inhalation Medication in Asthma-and COPD Patients.	Completed	NA	Interventional	2019-01-02
NCT01763463	WEUSKOP6416: Evaluating Pneumonia in Chronic Obstructive Pulmonary Disease (COPD) Subjects	Completed		Observational	2012-07
NCT03274791	Clinical Features and Airways Inflammation in Never Smokers and Smokers With COPD	Completed		Observational	2013-09
NCT02515318	Physiotherapy in Acute Exacerbation of Chronic Obstructive Pulmonary Disease	Unknown	NA	Interventional	2015-09
NCT06511193	Chronicling the COPD Patient Journey and Change in COPD Symptoms, Quality of Life and Exacerbations Following Initiation of Budenoside/Glycopyrronium/Formoterol [BGF]	Recruiting		Observational	2024-09-17
NCT02633280	Biomarkers for Diagnosis and Treatment of COPD	Completed		Observational	2016-04

Table 9: Hospitalization rates and patient-reported results in triple therapy for COPD management

Study	Patient population	Quality of life measure	Hospitalization rates	Key findings	References
IMPACT Trial	10,355 patients with moderate-to-severe COPD	Significant improvement in SGRQ score (−2.78)	Reduced annual rate of moderate/severe exacerbations (0.91 vs. 1.07)	Triple therapy reduced exacerbation rates by 15% compared to dual therapy	[105]
TRIBUTE Trial	1,532 patients with severe COPD	Improved health-related quality of life	Lower rate of moderate-to-severe exacerbations	Triple therapy lowered exacerbation rates by 15% compared to LAMA/lABA	[106]
ETHOS Trial	Patients with a history of frequent exacerbations	Enhanced quality of life indicators	Reduced risk of hospitalization due to exacerbations	Triple therapy showed significant reductions in exacerbation risk and improvements in quality of life	[107]

Clinical trials on COPD

Understanding the disease's pathophysiology and developing novel therapies have been the main goals of recent clinical studies on chronic obstructive pulmonary disease (COPD). There are many studies on COPD. Some of the studies on COPD are given in table 8.

Patient-reported outcomes and hospitalization rates in COPD Management with TRIPLE therapy

The following table summarizes various important patient-reported outcomes, such as quality of life and hospitalization rate, obtained from relevant clinical trials [91] on the effect of triple therapy for chronic obstructive pulmonary disease (COPD) management [104]. Hospitalization Rates and Patient-Reported Results in Triple Therapy for COPD Management are given in table 9.

CONCLUSION

Non-adherence to medication and poor clinical outcomes with improper maintenance therapy have raised the risk of severe attacks in COPD patients. To overcome such conditions, the use of a combinational approach containing three drugs in a single inhaler in the treatment regimen would have multiple benefits that provide significant bronchodilation, make breathing easier for severe COPD patients, and reduces the risk of severe attacks. According to a vast amount of clinical evidence, long-acting bronchodilators are helpful in stopping both moderate and severe exacerbations. Even though different mechanisms are involved in the bronchodilator effect on exacerbations, the most essential mechanism involves hyperinflation reduction and re-setting of lung function dynamics. LABA/lAMA FDCs have produced health benefits with active comparator inhaled medications, which have long been the gold standard of therapy for COPD. They have demonstrated better impacts on lung function than mono-component long-acting bronchodilator regimens.

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AUTHORS CONTRIBUTIONS

Preethi S: Conceptualization, Writing-original draft, Writing-review and editing, Data curation, Software and Methodology; Praveen Halagali: Writing-review and editing, Data curation and Software; Surya CS: Review, editing and revision of the work, Resources and Visualization; Vikas Jain: Conceptualization, Formal analysis, Project administration, Validation and Visualization. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTERESTS

Authors don't have any competing interest

REFERENCES

1. Quaderi SA, Hurst JR. The unmet global burden of COPD. Glob Health Epidemiol Genom. 2018 Apr 6;3:e4. doi: 10.1017/gheg.2018.1, PMID 29868229.
2. Rahmad, Narasati S, Nugroho E, Witjaksono D, Lestari DI, Nugroho MB. The role of pulmonary rehabilitation in acute exacerbations of chronic obstructive pulmonary disease. Int J App Pharm. 2020;12(3):39-40. doi: 10.22159/ijap.2020.v12s3.39466.
3. Khan S, Monika. Circadian rhythms regulated asthma treatment by virtue of pulsatile drug delivery system. Int J Appl Pharm. 2022;14(4):1-8. doi: 10.22159/ijap.2022v14i4.44395.
4. Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. Lancet. 2022 Jun 11;399:2227-42. doi: 10.1016/S0140-6736(22)00470-6, PMID 35533707.
5. Qureshi H, Sharafkhaneh A, Hanania NA. Chronic obstructive pulmonary disease exacerbations: latest evidence and clinical implications. Ther Adv Chronic Dis. 2014;5(5):212-27. doi: 10.1177/2040622314532862, PMID 25177479.
6. LE Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. J Am Coll Cardiol. 2007 Jan 16;49(2):171-80. doi: 10.1016/j.jacc.2006.08.046, PMID 17222727.
7. Barnes PJ. Muscarinic receptor subtypes: implications for therapy. Agents Actions. 1993;43:243-52. doi: 10.1007/978-3-0348-7324-6_21, PMID 8368167.
8. Haddad EB, Mak JC, Barnes PJ. Characterization of [3H] Ba 679 BR a slowly dissociating muscarinic antagonist in human lung: radioligand binding and autoradiographic mapping. Mol Pharmacol. 1994 May;45(5):899-907. PMID 8190106.
9. Skolnik NS, Nguyen TS, Shrestha A, Ray R, Corbridge TC, Brunton SA. Current evidence for COPD management with dual long-acting muscarinic antagonist/long-acting β2-agonist bronchodilators. Post Grad Med. 2020 Mar;132(2):198-205. doi: 10.1080/00325481.2019.1702834, PMID 31900019.
10. Wedzicha JA, Decramer M, Seemungal TA. The role of bronchodilator treatment in the prevention of exacerbations of COPD. Eur Respir J. 2012 Jul 26;40(6):1545-54. doi: 10.1183/09031936.00048912, PMID 22835613.
11. Beeh KM. The role of bronchodilators in preventing exacerbations of chronic obstructive pulmonary disease. Tuberc Respir Dis (Seoul). 2016;79(4):241-7. doi: 10.4046/trd.2016.79.4.241, PMID 27790275.
12. Singh D, Donohue JF, Boucot IH, Barnes NC, Compton C, Martinez FJ. Future concepts in bronchodilation for COPD: dual versus monotherapy. Eur Respir Rev. 2021 Jun 1;30(160):210023. doi: 10.1183/16000617.0023-2021, PMID 34415847.
13. Soler Cataluna JJ, Marzo M, Catalan P, Miralles C, Alcazar B, Miravitlles M. Validation of clinical control in COPD as a new tool for optimizing treatment. Int J COPD. 2018 Nov 14;13:3719-31. doi: 10.2147/COPD.S178149, PMID 30532528.
14. Vogelmeier CF, Roman Rodriguez M, Singh D, Han ML, Rodriguez Roisin R, Ferguson GT. Goals of COPD treatment: focus on symptoms and exacerbations. Respir Med. 2020 May;166:105938. doi: 10.1016/j.rmed.2020.105938, PMID 32250871.
15. O Driscoll BR, Babu KS, Chauhan AJ. Management of chronic obstructive pulmonary disease. BMJ. 2003 Apr 12;326:821. doi: 10.1136/bmj.326.7393.821, PMID 12689985.
16. Safka KA, Andrew McIvor R. Non-pharmacological management of chronic obstructive pulmonary disease. Ulster Med J. 2015 Jan;84(1):13-21. PMID 25964698.
17. Alagha K, Palot A, Sofalvi T, Pahus L, Gouitaa M, Tummino C. Long-acting muscarinic receptor antagonists for the treatment of chronic airway diseases. Ther Adv Chronic Dis. 2014;5(2):85-98. doi: 10.1177/2040622313518227, PMID 24587893.
18. KO FW, Chan KP, Hui DS, Goddard JR, Shaw JG, Reid DW. Acute exacerbation of COPD. Respirology. 2016 Oct;21(7):1152-65. doi: 10.1111/resp.12780, PMID 27028990.
19. Welte T. Optimising treatment for COPD new strategies for combination therapy. Int J Clin Pract. 2009 Aug;63(8):1136-49. doi: 10.1111/j.1742-1241.2009.02139.x, PMID 19624783.
20. Hunninghake GM, Cho MH, Tesfaigzi Y, Soto Quiros ME, Avila L, Lasky SU J. MMP12 lung function and COPD in high-risk populations. N Engl J Med. 2009;361(27):2599-608. doi: 10.1056/nejmoa0904006, PMID 20018959.
21. Venkatesan P. GOLD COPD report: 2023 update. Lancet Respir Med. 2023 Jan;11(1):18. doi: 10.1016/S2213-2600(22)00494-5, PMID 36462509.
22. Lokke A, Nielsen LP, Moberg M, Marsa K, Titlestad IL, Kofod LM. Treatment of stable chronic obstructive pulmonary disease. Ugeskr Laeger. 2019;180:2-6. doi: 10.2147/copd.s3483, PMID 19281074.
23. Wedzicha JA, Decramer M, Seemungal TA. The role of bronchodilator treatment in the prevention of exacerbations of COPD. Eur Respir J. 2012 Dec;40(6):1545-54. doi: 10.1183/09031936.00048912, PMID 22835613.
24. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA. Triple inhaled therapy at two glucocorticoid doses in moderate to very severe COPD. N Engl J Med. 2020;383(1):35-48. doi: 10.1056/nejmoa1916046, PMID 32579807.
25. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC. Once daily single inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018 May;378(18):1671-80. doi: 10.1056/nejmoa1713901, PMID 29668352.
26. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA. A phase III study of triple therapy with budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler 320/18/9.6 µg and 160/18/9.6 µg using co-suspension delivery technology in moderate to very severe COPD: the ETHOS study protocol. Respir Med. 2019 Oct;158:59-66. doi: 10.1016/j.rmed.2019.08.010, PMID 31605923.
27. D Urzo AD, Singh D, Donohue JF, Chapman KR, Wise RA. Aclidinium bromide/formoterol fumarate as a treatment for COPD: an update. Expert Rev Respir Med. 2021 Sep;15(9):1093-106. doi: 10.1080/17476348.2021.1920403, PMID 34137664.
28. King P. Role of arformoterol in the management of COPD. Int J COPD. 2008 Sep;3(3):385-92. doi: 10.2147/copd.s753, PMID 18990965.
29. Zheng J, XU JF, Jenkins M, Assam PN, Wang L, Lipworth BJ. Glycopyrrolate/formoterol fumarate metered dose inhaler for maintenance naive patients with chronic obstructive pulmonary disease: a post hoc analysis of the randomized PINNACLE trials. Respir Res. 2020 Mar 12;21(1):69. doi: 10.1186/s12931-020-1332-3, PMID 32164675.
30. Cazzola M, Bardaro F, Stirpe E. The role of indacaterol for chronic obstructive pulmonary disease (COPD). J Thorac Dis. 2013;5:559-66. doi: 10.3978/j.issn.2072-1439.2013.07.35, PMID 23991316.
31. Olodaterol another LABA for COPD. Drug Ther Bull. 2015;53:42-5. doi: 10.1136/dtb.2015.4.0319, PMID 25858815.
32. Tashkin DP, Ohar JA, Koltun A, Allan R, Ward JK. The role of ICS/lABA fixed-dose combinations in the treatment of asthma and COPD: bioequivalence of a generic fluticasone propionate salmeterol device. Pulm Med. 2021 Mar 17;2021:8881895. doi: 10.1155/2021/8881895, PMID 33815843.
33. Anzueto A, Miravitlles M. Tiotropium in chronic obstructive pulmonary disease a review of clinical development. Respir Res. 2020 Jul 29;21(1):199. doi: 10.1186/s12931-020-01407-y, PMID 32727455.
34. Umeclidinium. Another LAMA for COPD. Drug Ther Bull. 2015;53(7):81-4. doi: 10.1136/dtb.2015.7.0340, PMID 26159701.

35. Yang IA, Brown JL, George J, Jenkins S, MC Donald CF, MC Donald VM. COPD-X australian and new zealand guidelines for the diagnosis and management of chronic obstructive pulmonary disease: 2017 update. Med J Aust. 2017 Nov 20;207(10):436-42. doi: 10.5694/mja17.00686, PMID 29129177.
36. Singh D. Pharmacological treatment of stable chronic obstructive pulmonary disease. Respirology. 2021 Jul;26(7):643-51. doi: 10.1111/resp.14046, PMID 33829619.
37. Van Der Molen T, Cazzola M. Beyond lung function in COPD management: effectiveness of LABA/lAMA combination therapy on patient-centred outcomes. Prim Care Respir J. 2012;21(1):101-8. doi: 10.4104/pcrj.2011.00102, PMID 22222945.
38. Pennington E, Bell S, Hill JE. Should video laryngoscopy or direct laryngoscopy be used for adults undergoing endotracheal intubation in the pre-hospital setting? a critical appraisal of a systematic review. J Paramed Pract. 2023;15(6):255-9. doi: 10.1002/14651858, PMID 38812899.
39. Janson C. Treatment with inhaled corticosteroids in chronic obstructive pulmonary disease. J Thorac Dis. 2020;12(4):1561-9. doi: 10.21037/jtd.2020.02.51, PMID 32395293.
40. Tashkin D, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S. A 4 y trial of tiotropium in chronic obstructive pulmonary disease (UPLIFT trial). Rev Port Pneumol. 2009;15(1):137-40. doi: 10.1016/S0873-2159(15)30121-5, PMID 25965528.
41. Tashkin DP, Ohar JA, Koltun A, Allan R, Ward JK. The role of ICS/lABA fixed-dose combinations in the treatment of asthma and COPD: bioequivalence of a generic fluticasone propionate salmeterol device. Pulm Med. 2021 Mar 17;2021:8881895. doi: 10.1155/2021/8881895, PMID 33815843.
42. Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable and fixed-dose budesonide/formoterol pressurized metered dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. J Allergy Clin Immunol. 2008 Jun;121(6):1407-14. doi: 10.1016/j.jaci.2008.03.019, PMID 18455221.
43. Berger WE. Mometasone furoate/formoterol in the treatment of persistent asthma. Expert Rev Respir Med. 2011 Dec;5(6):739-46. doi: 10.1586/ers.11.71, PMID 22082160.
44. Syed YY. Fluticasone furoate/vilanterol: a review of its use in patients with asthma. Drugs. 2015 Mar;75(4):407-18. doi: 10.1007/s40265-015-0354-5, PMID 25648266.
45. Mc Keage K, Keam SJ. Salmeterol fluticasone propionate: a review of its use in asthma. Drugs. 2009;69(13):1799-828. doi: 10.2165/11202210-000000000-00000, PMID 19719334.
46. Van Noord JA, Aumann JL, Janssens E, Smeets JJ, Zaagsma J, Mueller A. Combining tiotropium and salmeterol in COPD: effects on airflow obstruction and symptoms. Respir Med. 2010 Jul;104(7):995-1004. doi: 10.1016/j.rmed.2010.02.017, PMID 20303247.
47. Vogelmeier C, Kardos P, Harari S, Gans SJ, Stenglein S, Thirlwell J. Formoterol mono and combination therapy with tiotropium in patients with COPD: A 6-month study. Respir Med. 2008;102:1511-20. doi: 10.1016/j.rmed.2008.07.020, PMID 18804362.
48. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease: beclometasone formoterol and glycopyrronium (Trimbow). Nice Advice; 2018. p. 1-78.
49. Richeldi L, Piraino A, Macagno F, Micarelli G, Ingrassia E. The impact of fixed triple therapy with beclometasone/formoterol/glycopyrronium on health status and adherence in chronic obstructive pulmonary disease (COPD) in an Italian context of real life: the tritrial study protocol. Int J COPD. 2021 Jan 27;16:159-66. doi: 10.2147/COPD.S286559, PMID 33536751.
50. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (Tribute): a double-blind parallel group randomized controlled trial. Lancet. 2018 Mar 17;391(10125):1076-84. doi: 10.1016/S0140-6736(18)30206-X, PMID 29429593.
51. Mahler DA, Buhl R, Lawrence D, MC Bryan D. Efficacy and safety of indacaterol and tiotropium in COPD patients according to dyspnoea severity. Pulm Pharmacol Ther. 2013 Jun;26(3):348-55. doi: 10.1016/j.pupt.2013.02.006, PMID 23434446.
52. Mahler DA, D Urzo A, Bateman ED, Ozkan SA, White T, Peckitt C. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised double-blind comparison. Thorax. 2012;67(9):781-8. doi: 10.1136/thoraxjnl-2011-201140, PMID 22544891.
53. D Urzo A, Rennard S, Kerwin E, Donohue JF, Lei A, Molins E. A randomised double-blind placebo-controlled long-term extension study of the efficacy safety and tolerability of fixed dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease. Respir Med. 2017 Apr;125:39-48. doi: 10.1016/j.rmed.2017.02.008, PMID 28340861.
54. Ferguson GT, Taylor AF, Thach C, Wang Q, Schubert Tennigkeit AA, Patalano F. Long-term maintenance bronchodilation with indacaterol/glycopyrrolate versus indacaterol in moderate to severe COPD patients: the FLIGHT 3 study. Chronic Obstr Pulm Dis. 2016;3(4):716-28. doi: 10.15326/jcopdf.3.4.2016.0131, PMID 28848898.
55. O Donnell DE, Casaburi R, Frith P, Kirsten A, DE Sousa D, Hamilton A. Effects of combined tiotropium/olodaterol on inspiratory capacity and exercise endurance in COPD. Eur Respir J. 2017 Apr 19;49(4):1601348. doi: 10.1183/13993003.01348-2016, PMID 28424359.
56. Maltais F, Singh S, Donald AC, Crater G, Church A, Goh AH. Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized double-blind clinical trials. Ther Adv Respir Dis. 2014 Dec;8(6):169-81. doi: 10.1177/1753465814559209, PMID 25452426.
57. Martinez FJ, Rabe KF, Ferguson GT, Fabbri LM, Rennard S, Feldman GJ. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. Chest. 2017 Feb;151(2):340-57. doi: 10.1016/j.chest.2016.11.028, PMID 27916620.
58. Jung KS, Park HY, Park SY, Kim SK, Kim YK, Shim JJ. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. Respir Med. 2012 Mar;106(3):382-9. doi: 10.1016/j.rmed.2011.09.004, PMID 21975275.
59. Chatterjee A, Shah M, D Souza AO, Bechtel B, Crater G, Dalal AA. Observational study on the impact of initiating tiotropium alone versus tiotropium with fluticasone propionate/salmeterol combination therapy on outcomes and costs in chronic obstructive pulmonary disease. Respir Res. 2012 Feb 17;13(1):15. doi: 10.1186/1465-9921-13-15, PMID 22340019.
60. Singh D, Brooks J, Hagan G, Cahn A, O Connor BJ. Superiority of triple therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. Thorax. 2008 Jul;63(7):592-8. doi: 10.1136/thx.2007.087213, PMID 18245142.
61. Maltais F, Hamilton A, Voß F, Maleki Yazdi MR. Dose determination for a fixed dose drug combination: a phase II randomized controlled trial for tiotropium/olodaterol versus tiotropium in patients with COPD. Adv Ther. 2019 Apr;36(4):962-8. doi: 10.1007/s12325-019-00911-y, PMID 30843141.
62. Bogart M, Stanford RH, Laliberte F, Germain G, WU JW, Duh MS. Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. Int J COPD. 2019 Feb 19;14:343-52. doi: 10.2147/COPD.S184653, PMID 30863037.
63. Gaduzo S, MC Govern V, Roberts J, Scullion JE, Singh D. When to use single inhaler triple therapy in COPD: a practical approach for primary care health care professionals. Int J COPD. 2019 Feb13;14:391-401. doi: 10.2147/COPD.S173901, PMID 30863039.
64. Pascoe S, Barnes N, Brusselle G, Compton C, Criner GJ, Dransfield MT. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the impact trial. Lancet Respir Med. 2019 Sep;7(9):745-56. doi: 10.1016/S2213-2600(19)30190-0, PMID 31281061.

65. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts exacerbations and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med. 2015 Jun;3(6):435-42. doi: 10.1016/S2213-2600(15)00106-X, PMID 25878028.
66. Vanfleteren LE, Ullman A, Nordenson A, Andersson A, Andelid K, Fabbri LM. Triple therapy (ICS/lABA/lAMA) in COPD: thinking out of the box. ERJ Open Res. 2019;5(1):00185-2018. doi: 10.1183/23120541.00185-2018, PMID 30775372.
67. Ritondo BL, Puxeddu E, Calzetta L, Cazzola M, Rogliani P. Efficacy and safety of triple combination therapy for treating chronic obstructive pulmonary disease: an expert review. Expert Opin Pharmacother. 2021;22(5):611-20. doi: 10.1080/14656566.2020.1845314, PMID 33131340.
68. COPD global initiative. Global Initiative for Chronic Obstructive Lung Disease; 2020.
69. Singh D, Fabbri LM, Corradi M, Georges G, Guasconi A, Vezzoli S. Extrafine triple therapy in patients with symptomatic COPD and history of one moderate exacerbation. Eur Respir J. 2019 May 18;53(5):1900235. doi: 10.1183/13993003.00235-2019, PMID 30792343.
70. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C. Single inhaler extra fine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (trinity): a double-blind, parallel-group randomised controlled trial. Lancet. 2017 May 13;389(10082):1919-29. doi: 10.1016/S0140-6736(17)30188-5, PMID 28385353.
71. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (Tribute): a double blind, parallel-group randomised controlled trial. Lancet. 2018 Mar 17;391(10125):1076-84. doi: 10.1016/S0140-6736(18)30206-X, PMID 29429593.
72. Gross N. The COPD pipeline XXX. Chronic Obstr Pulm Dis. 2015;3(1):498-502. doi: 10.15326/jcopdf.3.1.2015.0181, PMID 28848873.
73. Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA. Fulfil trial: once daily triple therapy for patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017 Aug 15;196(4):438-46. doi: 10.1164/rccm.201703-0449OC, PMID 28375647.
74. Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind parallel-group multicentre phase 3 randomised controlled trial. Lancet Respir Med. 2018 Oct;6(10):747-58. doi: 10.1016/S2213-2600(18)30327-8, PMID 30232048.
75. Halpin DM, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ. Global initiative for the diagnosis, management and prevention of chronic obstructive lung disease. Am J Respir Crit Care Med. 2021;203(1):24-36. doi: 10.1164/rccm.202009-3533SO, PMID 33146552.
76. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C. Single inhaler extrafine triple therapy versus long acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (trinity): a double blind parallel group randomised controlled trial. Lancet. 2017 May 13;389(10082):1919-29. doi: 10.1016/S0140-6736(17)30188-5, PMID 28385353.
77. Tsiligianni I, Goodridge D, Marciniuk D, Hull S, Bourbeau J. Four patients with a history of acute exacerbations of COPD: implementing the chest/canadian thoracic society guidelines for preventing exacerbations. NPJ Prim Care Respir Med. 2015 May 7;25:15023. doi: 10.1038/npjpcrm.2015.23, PMID 25950092.
78. Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (Kronos): a double blind parallel group multicentre phase 3 randomised controlled trial. Lancet Respir Med. 2018 Oct;6(10):747-58. doi: 10.1016/S2213-2600(18)30327-8, PMID 30232048.
79. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA. Triple inhaled therapy at two glucocorticoid doses in moderate to very severe COPD. N Engl J Med. 2020;383:35-48. doi: 10.1056/nejmoa1916046, PMID 32579807.
80. YU AP, Guerin A, Ponce DE Leon D, Ramakrishnan K, WU EQ, Mocarski M. Therapy persistence and adherence in patients with chronic obstructive pulmonary disease: multiple versus single long-acting maintenance inhalers. J Med Econ. 2011;14(4):486-96. doi: 10.3111/13696998.2011.594123, PMID 21679019.
81. Gaduzo S, MC Govern V, Roberts J, Scullion JE, Singh D. When to use single inhaler triple therapy in COPD: a practical approach for primary care health care professionals. Int J COPD. 2019 Feb 13;14:391-401. doi: 10.2147/COPD.S173901, PMID 30863039.
82. Fabbri LM, Roversi S, Beghe B. Triple therapy for symptomatic patients with COPD. Lancet. 2017 May 13;389(10082):1864-5. doi: 10.1016/S0140-6736(17)30567-6, PMID 28385354.
83. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal Singer R. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363:1128-38. doi: 10.1056/nejmoa0909883, PMID 20843247.
84. Han ML, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the spiromics cohort. Lancet Respir Med. 2017 Aug;5(8):619-26. doi: 10.1016/S2213-2600(17)30207-2, PMID 28668356.
85. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Ann Intern Med. 2012 Dec 4;157(11):785-95. doi: 10.7326/0003-4819-157-11-201212040-00538, PMID 22964778.
86. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, Fitz Geralde M. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008 Jan;31(1):143-78. doi: 10.1183/09031936.00138707, PMID 18166595.
87. Bender BG. Nonadherence to asthma treatment: getting unstuck. J Allergy Clin Immunol Pract. 2016 Sep-Oct;4(5):849-51. doi: 10.1016/j.jaip.2016.07.007, PMID 27587318.
88. Mehta PP, Dhapte Pawar VS. Repurposing drug molecules for new pulmonary therapeutic interventions. Drug Deliv Transl Res. 2021 Oct;11(5):1829-48. doi: 10.1007/s13346-020-00874-6, PMID 33188495.
89. Mehta PP, Dhapte Pawar VS. Novel and evolving therapies for COVID-19 related pulmonary complications. Am J Med Sci. 2021 May;361(5):557-66. doi: 10.1016/j.amjms.2021.02.019, PMID 33640363.
90. Leung JM, Niikura M, Yang CW, Sin DD. COVID-19 and COPD. Eur Respir J. 2020 Aug 13;56(2):2002108. doi: 10.1183/13993003.02108-2020, PMID 32269089.
91. https://www.healthline.com/health/copd/drugs.
92. Cheyne L, Irvin Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015 Sep 22;2015(9):CD009592. doi: 10.1002/14651858, PMID 26391969.
93. Hanania NA, Donohue JF, Nelson H, Sciarappa K, Goodwin E, Baumgartner RA. The safety and efficacy of arformoterol and formoterol in COPD. COPD J Chronic Obstruct Pulm Dis. 2010 Feb;7(1):17-31. doi: 10.3109/15412550903499498, PMID 20214460.
94. Keating GM, MC Cormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. Drugs. 2007;67(16):2383-405. doi: 10.2165/00003495-200767160-00006, PMID 17983257.
95. Heo YA. Budesonide/Glycopyrronium/Formoterol: a review in COPD. Drugs. 2021 Aug;81(12):1411-22. doi: 10.1007/s40265-021-01562-6, PMID 34342835.
96. Cazzola M, Rogliani P, Stolz D, Matera MG. Pharmacological treatment and current controversies in COPD. F1000Res. 2019;8:F1000 Faculty Rev-1533. doi: 10.12688/f1000research.19811.1, PMID 31508197.

97. Lavorini F, Fontana GA, Usmani OS. New inhaler devices the good the bad and the ugly. Respiration. 2014;88(1):3-15. doi: 10.1159/000363390, PMID 24902629.
98. Ibrahim M, Verma R, Garcia Contreras L. Inhalation drug delivery devices: technology update. Med Devices Evid Res. 2015 Feb 12;8:131-9. doi: 10.2147/MDER.S48888, PMID 25709510.
99. Labiris NR, Dolovich MB. Pulmonary drug delivery part II: the role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications. Br J Clin Pharmacol. 2003 Dec;56(6):600-12. doi: 10.1046/j.1365-2125.2003.01893, PMID 14616419.
100. Park H, Otte A, Park K. Evolution of drug delivery systems: from 1950 to 2020 and beyond. J Control Release. 2022 Feb;342:53-65. doi: 10.1016/j.jconrel.2021.12.030, PMID 34971694.
101. Adepu S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. Molecules. 2021;26(19):5905. doi: 10.3390/molecules26195905, PMID 34641447.
102. Hardinge M, Rutter H, Velardo C, Shah SA, Williams V, Tarassenko L. Using a mobile health application to support self management in chronic obstructive pulmonary disease: a six month cohort study eHealth/telehealth/mobile health systems AC-63541e8b0e2a0d7170bcd513bb89d0cf. BMC Med Inform Decis Mak. 2015;15. doi: 10.1186/s12911-015-0171-5, PMID 26084626.
103. https://clinicaltrials.gov/search?intr=bronchodilators%20in%20the%20treatment%20of%20COPD. [Last accessed on 06 Feb 2025].
104. Miravitlles M, Acharya S, Aggarwal B, Fernandes FL, Jardim JR, Juthong S. Clinical concepts for triple therapy use in patients with COPD: a delphi consensus. Int J COPD. 2023;18:1853-66. doi: 10.2147/COPD.S424128, PMID 37662490.
105. Kato M, Tomii K, Hashimoto K, Nezu Y, Ishii T, Jones CE. The Impact study single inhaler triple therapy (FF/UMEC/VI) versus FF/VI and UMEC/VI in patients with COPD: efficacy and safety in a Japanese population. Int J COPD. 2019;14:2849-61. doi: 10.2147/COPD.S226601, PMID 31839705.
106. Tan DJ, Van Geffen WH, Walters EH. Impact of triple therapy vs dual bronchodilator therapy on mortality rates in COPD. Chest. 2024;165:e158-9. doi: 10.1016/j. chest.2023.12.033, PMID 38724158.
107. Esteban C, Arostegui I, Aramburu A, Moraza J, Aburto M, Aizpiri S. Changes in health related quality of life as a marker in the prognosis in COPD patients. ERJ Open Res. 2022 Jan 10;8(1):00181-2021. doi: 10.1183/23120541.00181-2021, PMID 35036422.