

## MANAGEMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE : A SYSTEMATIC REVIEW

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### Abstract

**Introduction:** The goal of drug treatment for chronic obstructive pulmonary disease (COPD) is to relieve symptoms and lower the chance of future problems like flare-ups, disease progression, and death. Because COPD is not all the same, people respond differently to drug treatments. The best way to treat COPD now is with precision medicine, which uses clinical and biomarker data to make treatment decisions that are best for each person.

**The aim:** This article discusses management of stable chronic obstructive pulmonary disease.

**Methods:** By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

**Result:** In the PubMed database, the results of our search brought up 68 articles, whereas the results of our search on SagePub brought up 32 articles. The results of the search conducted for the last year of 2013 yielded a total 31 articles for PubMed and 15 articles for SagePub. In the end, we compiled a total of 14 papers, 10 of which came from PubMed and four of which came from SagePub. We included four research that met the criteria.

**Conclusion:** COPD treatment has evolved to match clinical characteristics and biomarkers to each patient. Hospitalizations and death have improved in triple combination treatment studies. However, COPD treatments are lacking, such as emphysema-slowing drugs. Despite progress, much remains.

**Keyword:** Broncodhilator; Chronic obstructive pulmonary disease; Corticosteroids

**INTRODUCTION**

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disease that affects millions of people worldwide, causing a significant increase in admission rates.<sup>1</sup> The World Health Organization (WHO) estimates that COPD will be the third leading cause of death globally by 2020. These patients are also very large users of health and social services resources. There is no cure for COPD, so self-care and appropriate management play an important role in a patient's life.<sup>2</sup> COPD is the largest contributor to morbidity (35%) due to lung disease in Indonesia, followed by bronchial asthma (33%), lung cancer (30%), and others (2%).<sup>3</sup>

Cigarettes are the main cause of COPD in developed countries, while firewood and charcoal smoke are in developing countries. The pathogenesis of COPD is closely related to the effects of cigarette smoke on the lungs, where a relationship is found between the number of cigarettes and the severity of COPD.<sup>2</sup> Chronic obstructive pulmonary disease (COPD) is associated with impaired pulmonary inflammatory response caused by inhalation produced by cigarette smoke, air pollution, or exposure received at work. All smokers experience lung inflammation that continues to increase and does not improve after stopping smoking.<sup>4,5</sup>

The Global Burden of Disease Study reported a prevalence of 251 million cases of COPD globally in 2016 and an estimated 3.17 million deaths due to COPD in 2015 (i.e., 5% of all deaths globally). More than 90% of COPD deaths occur in low- and middle-income countries.<sup>6</sup> The increase in the incidence of COPD is due to demographic changes and increasing life expectancy.<sup>7</sup> However, COPD is also not uncommon in non-smokers. Another study found that the prevalence of COPD in people who had never smoked was 3.0-7%.<sup>8</sup>

This page provides information about management of stable chronic obstructive pulmonary disease.

**METHODS**

**Protocol**

The author of this study made sure it met the standards by following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 rules. This is done to make sure that the results of the investigation are correct.

**Criteria for Eligibility**

In this literature review, we talk about management of stable chronic obstructive pulmonary disease. As the main goal of this piece of writing, showing how the problems that have been outlined are important will happen throughout the whole thing. For experts to be able to take part in the study, they had to meet the following requirements: 1) The paper needs to be written in English, and it will be about management of stable chronic obstructive pulmonary disease. The manuscript needs to meet both of these standards before it can be considered for publication. 2) Several of the papers that were looked at came out after 2013, but before the time period that this systematic review thinks is important. Editorials, proposals without a DOI, review articles that have already been published, and entries that are almost exactly the same as journal papers that have already been published are all types of studies that are not allowed.

**Search Strategy**

We used "management"; "stable"; and "chronic obstructive pulmonary disease" as keywords. The search for studies to be included in the systematic review was carried out from August 5<sup>th</sup> 2023 using the PubMed and SagePub databases by inputting the words: (*"manage"[All Fields] OR "managed"[All Fields] OR "management s"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "managment"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields] AND ("stable"[All Fields] OR "stabled"[All Fields] OR "stables"[All Fields] OR "stabling"[All Fields]) AND ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields] AND "obstructive"[All Fields] AND "pulmonary"[All Fields] AND "disease"[All Fields])) AND ((y\_10[Filter]) AND (clinicaltrial[Filter])) used in searching the literature.*

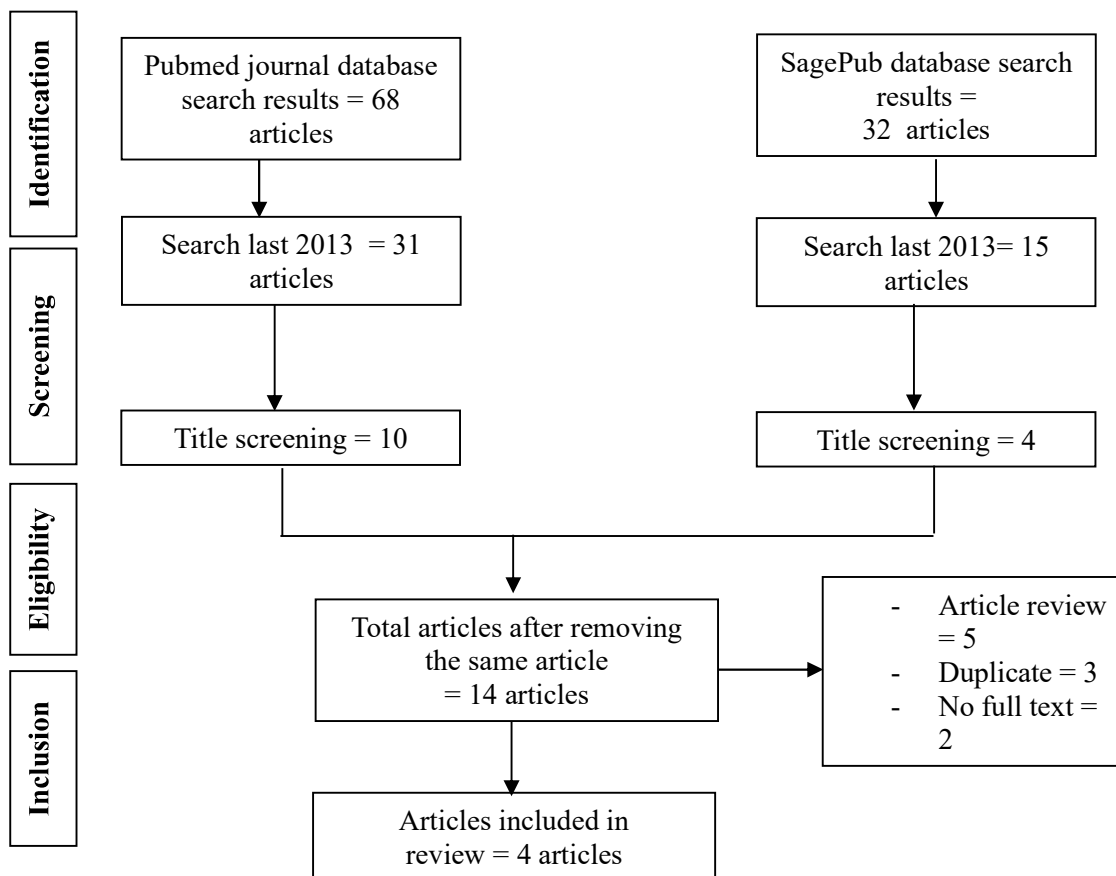


Figure 1. Article search flowchart

**Data retrieval**

The writers looked at each study's abstract and title to see if it met the inclusion standards. The writers then chose which studies from earlier research they wanted to use as sources for their piece. This conclusion was made after looking at a lot of different studies that all seemed to point to the same trend. All entries must be written in English and can't have been seen anywhere else.

For the systematic review, only studies that met all of the criteria for inclusion were taken into account. This narrows down the list of results to only those that match the search. We don't take into account the results of any study that doesn't meet our standards. After that, the study results will be looked at in great depth. As a result of the research that was done for this study, the following pieces of material were found: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Before deciding which publications to look into more, each author did their own research on the research that was in the title and summary of the publication. The next step will be to evaluate all of the articles that can be included in the review because they meet the criteria set up for that reason in the review. After that, based on what we've found, we'll decide which pieces to include in the review. This measure is used to choose papers that will be looked at more closely. So as to make the process of choosing papers to assess as easy as possible. Here, we talk about what research was done in the past and what about those studies made it right to include them in the review.

**RESULT**

In the PubMed database, the results of our search brought up 68 articles, whereas the results of our search on SagePub brought up 32 articles. The results of the search conducted for the last year of 2013 yielded a total 31 articles for PubMed and 15 articles for SagePub. In the end, we compiled a total of 14 papers, 10 of which came from PubMed and four of which came from SagePub. We included four research that met the criteria.

Rabe, et al (2020)<sup>9</sup> showed annual rates of moderate or severe exacerbations were 1.08 in the budesonide 320-µg triple-therapy group (2137 patients), 1.07 in the budesonide 160- µg triple-therapy group (2121 patients), 1.42 in the glycopyrrolate-formoterol group (2120 patients), and 1.24 in the budesonide-formoterol group (2131 patients). The rate was significantly lower with 320 µg budesonide triple therapy than with glycopyrrolate-formoterol (P <0.001; rate ratio [RR] = 0.76; 95% confidence interval [CI] = 0.69 to 0.83; P <0.001) or budesonide-formoterol (P = 0.003).

**Table 1. The literature include in this study**

Author	Origin	Method	Sample Size	Result
Rabe, 2020 <sup>9</sup>	Sweden	Randomized controlled trial	8,509 patients with COPD	In comparison to glycopyrrolate-formoterol or budesonide-formoterol, triple therapy with twice-daily budesonide (at either the 160-µg or 320-µg dose), glycopyrrolate, and formoterol resulted in a lower rate of moderate or severe COPD exacerbations.
Lipson, 2018 <sup>10</sup>	United State of America	Randomized controlled trial	10,355 patients with COPD	In comparison to fluticasone furoate-vilanterol or umeclidinium-vilanterol, triple therapy with fluticasone furoate, umeclidinium, and vilanterol had a lower rate of moderate or severe COPD exacerbations in this population. A reduced rate of COPD-related hospitalizations was seen with triple therapy than with umeclidinium-vilanterol.
Bremner, 2018 <sup>11</sup>	Australia	Randomized controlled trial	1,055 patients with COPD	On the trough FEV1 change from baseline at 24 weeks, single-inhaler triple treatment (FF/UMEC/VI) is non-inferior to two inhalers (FF/VI + UMEC). On all other effectiveness, health-related quality of life, and safety metrics, the findings were consistent.
Dransfield, 2013 <sup>12</sup>	United State of America	Randomized controlled trial	1,622 patients with COPD	In patients with a previous history of COPD exacerbation, adding fluticasone furoate to vilanterol was related with a lower rate of moderate and severe COPD exacerbations. However, this was also associated with an increased risk of pneumonia.

Similarly, the rate was significantly lower with 160- µg -budesonide triple therapy than with glycopyrrolate-formoterol (25 percent lower: RR = 0.75; 95% CI = 0.69 to 0.83; P <0.001) or budesonide-formoterol (14 percent lower: RR = 0.86; 95% CI = 0.79 to 0.95; P = 0.002). The incidence of adverse events was comparable across treatment groups (range, 61.7% to 64.5%); the incidence of confirmed pneumonia ranged from 3.5% to 4.5% in the inhaled glucocorticoid groups and was 2.3% in the glycopyrrolate-formoterol group.<sup>9</sup>

Lipson, et al (2018)<sup>10</sup> showed the rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate-vilanterol group (rate ratio [RR] with triple therapy = 0.85; 95% confidence interval [CI] = 0.80-0.90; 15% difference; P <0.001) and 1.21 per year in the umeclidinium-vilanterol group (RR with triple therapy, 0.75; 95% CI = 0.70 to 0.81; 25% difference; P <0.001).

In the triple-therapy group, the annual rate of severe exacerbations leading to hospitalization was 0.13, as opposed to 0.19 in the umeclidinium-vilanterol group (RR = 0.66; 95% CI = 0.56-0.78; 34% difference; P <0.001). The risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium-vilanterol, as determined by a time-to-first-event analysis (hazard ratio [HR] = 1.53; 95% CI = 1.22 to 1.92; P <0.001). The incidence of pneumonia was higher in the inhaled-glucocorticoid groups than in the umeclidinium-vilanterol group.<sup>10</sup>

Bremner, et al (2018)<sup>11</sup> showed median difference in trough FEV1 from baseline at Week 24 for fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) and FF/VI + UMEC, respectively, was 113 mL (95% CI = 91-135) and 95 mL (95% CI = 72-117); the between-treatment difference of 18 mL (95% CI = -13-50), which verified FF/UMEC/VI's was regarded non-inferior to FF/VI + UMEC. At Week 24, the percentage of respondents based on St George's Respiratory Questionnaire Total score was 50% (FF/UMEC/VI) and 51% (FF/VI + UMEC).

The percentage of respondents based on Transitional Dyspnea Index focused score was comparable (56% both groups). In both the FF/VI + UMEC (27%) and FF/VI + UMEC (24%) groups, a similar percentage of patients suffered a moderate/severe exacerbation; the hazard ratio for time to first moderate/severe exacerbation with FF/UMEC/VI versus FF/VI + UMEC was 0.87 (95% CI = 0.68-1.12). While both groups (48%) experienced adverse events, only 10% (FF/UMEC/VI) and 11% (FF/VI + UMEC) experienced major adverse events.<sup>11</sup>

Dransfield, et al (2013)<sup>12</sup> showed significantly fewer moderate and severe exacerbations were noted in all fluticasone furoate/vilanterol groups than in the vilanterol only group (p=0.0398 for the 50 µg group, 0.0244 for the 100 µg group, and 0.0004 for the 200 µg group). In the pooled analysis, significantly fewer moderate and severe exacerbations were noted in all fluticasone furoate/vilanterol groups than in the vilanterol only group (0.0141 for the 50 µg group, <0.0001 for the 100 µg group, and 0.0003 for the 200 µg group). Nasopharyngitis was the most frequently reported adverse event in both studies. Pneumonia and fractures were reported more frequently with fluticasone furoate and vilanterol than with vilanterol alone. Eight deaths from pneumonia were noted in the fluticasone furoate/vilanterol groups compared with none in the vilanterol only group.

## DISCUSSION

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disorder characterized by airflow limitation and an increased chronic inflammatory response in the airways. The frequent comorbidities in COPD have a significant impact on patient quality of life, exacerbation frequency, and survival.<sup>2</sup> COPD in the acute exacerbation phase is a condition in which chronic obstructive pulmonary disease experiences a sudden worsening of the course of the disease caused by a precipitating factor and is characterized by aggravating clinical manifestations.<sup>1</sup>

Inhaled bronchodilators are prescribed to patients with stable COPD, unless the preparations are not accessible or cannot be afforded. These medications may be used continuously (if symptoms continue) or only as needed (if symptoms come and go). Three classes can be given, including:  $\beta$ -2 agonists (fenoterol, salbutamol, albuterol, terbutaline, formoterol, salmeterol), anticholinergics: (ipratropium bromide, oxytropium bromide), and methylxanthin (slow-release theophylline, if the combination of  $\beta$ -2 and steroids are not satisfactory).<sup>13-15</sup>

Folmetrol and salmeterol are LABAs given 2 times a day, which significantly improve FEV1 and lung volume, tightness, exacerbation rate and number of hospital admissions, but there is no effect on improving mortality or lung function. Indacaterol or LABA consumed once a day can improve tightness, health status, and the rate of exacerbations. Some patients with a history of coughing will be followed by indacaterol inhalation. Oladaterol and vilanterol are additional LABAs that can be consumed once a day and can improve symptoms and lung function.<sup>16</sup>

COPD that shows a response to steroid tests is given with VEPI <50% prediction (grades III and IV) and acute exacerbations. In COPD patients, treatment with ICS shows a limited response. Several drugs including beta2-agonists, theophylline or macrolides can affect corticosteroid sensitivity in COPD. Treatment with ICS alone cannot modify the decrease in FEV1.<sup>17,18</sup> In patients with moderate-severe COPD, the combination of ICS with LABA is more effective in improving lung function, health status and reducing exacerbations. In addition, treatment with LABA/ICS fixed dose combination (FDC) has a significant effect compared to LABA alone, in patients with exacerbations a maximum of once a year.<sup>19</sup>

Patients with moderate COPD, ICS therapy alone or in combination with LABA, does not increase the risk of pneumonia. Several studies have shown an increased risk of fracture and decreased bone density on ICS therapy. In addition, ICS therapy may be associated with an increased risk of diabetes, cataracts, and mycobacterial infections including TB. Effects of ICS withdrawal, depending on pulmonary function, symptoms and exacerbations. Increased exacerbations and/or symptoms followed by withdrawal effects of ICS. Decreased FEV1 (40 ml) with withdrawal from ICS is associated with an increased eosinophil threshold.<sup>13,19,20</sup>

Ambroxol, carbocysteine, and glycerol iodide are other mucolytics. N-Acetyl-cysteine antioxidants. Immunoregulators and antitussives, but seldom. Antimuscarinics prevent acetylcholine from constricting respiratory tract smooth muscles at M3 receptors. Short-acting antimuscarinics (SAMAS) like ipratropium and oxitropium inhibit M2 neuronal receptors, causing bronchoconstriction. Tiotropium, aclidinium, glycopyrronium bromide, and umeclidinium, long-acting muscarinic antagonists (LAMAS), bind to M3 receptors faster than M2 receptors, prolonging the bronchodilator effect.<sup>13,21</sup>

Ipratropium, a short-acting muscarinic antagonist, improves lung function, health, and oral steroid use less than beta2-agonists. Tiotropium, umeclidinium, aclidinium, and glycopyrronium are all given once a day, however some countries give them twice.<sup>13,21</sup> Antibiotics against S pneumoniae, H influenza, M catarrhalis. Several studies have shown that regular use of antibiotics can reduce the rate of exacerbations. Azithromycin (250 mg/day or 500 mg 3 times per week) or erythromycin (500 mg 2 times per day) for one year may reduce the risk of exacerbations. Azithromycin is associated with an increased incidence of bacterial resistance and hearing loss.<sup>22</sup>

Long-term use of steroids increases the risk of bone loss, aka osteoporosis. In these conditions it is dangerous to cause fractures, and increase the risk of death or spinal fracture. In patients with stable COPD, using inhaled steroids for more than six months may induce oropharyngeal candidiasis, hoarseness, and an increased risk of pneumonia, but it did not raise the risk of death, osteoporosis, or fractures.<sup>13,23</sup>

## CONCLUSION

COPD treatment has evolved to match clinical characteristics and biomarkers to each patient. Hospitalizations and death have improved in triple combination treatment studies. However, COPD treatments are lacking, such as emphysema-slowing drugs. Despite progress, much remains.

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